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HOSAR25	305	509226	1 - 319	15 - 333	
HOSBR08	306	925430	1 - 94	15 - 108	
HOSBU17	307	667195	1 - 569	15 - 583	AA181322.
HOSBU81	308	508735	1 - 156	15 - 170	
HOSBV22	309	780092	1 - 252	15 - 266	AI368409, AI767148, AI347671, AI400068, AA954702, AI583977, AA009615, AI418746, and AI457713.
HOSBW16	310	933016	1 - 238	15 - 252	AA421843.
HOSCG51	311	967584	1 - 421	15 - 435	AA381761.
HOSCM15	312	921336	1 - 384	15 - 398	AC005661.
HOSCZ35	313	707379	1 - 356	15 - 370	AA330344, and AJ005821.
HOSDE63	314	580959	1 - 188	15 - 202	HI15344, AI752743, R23438, AA401585, AW339993, Z44943, H06750, H50269, and H40825.
HOSDG51	315	523872	1 - 359	15 - 373	
HOSDN27	316	530459	1 - 256	15 - 270	
HOSEB61	317	741812	1 - 883	15 - 897	N98675, and AL049781.
HOSEM84	318	831049	1 - 354	15 - 368	AI073997, H87655, AA326173, AA157664, W45610, AA182685, AA352875, AA358040, and AA320365.
HOSFO57	319	736034	1 - 309	15 - 323	AW363743.
HOSFV63	320	873010	1 - 159	15 - 173	R32290, H56316, H56315, AI701812, AI818182, H02802, AW189354, AA179098, AI149010, AA903771, AA846152, AW236253, AI688210, AA219082, AI188637, AI457307, AW148946, AI912534, AW008419, AW149032, W56627, AA470757, AA464507, AI888588, AI056698, AW168755, AI924212, AA522891, AW089716, AW193562, AA987677, AA343171, AA769724, F35157, and AA361146.
HOSFY79	321	774052	1 - 417	15 - 431	
HOSFZ39	322	705351	1 - 355	15 - 369	
HOSGH28	323	686649	1 - 395	15 - 409	AA364637, AA149539, AA405966, AA828153, AI032490, AA320105, AA237098, AA662590, H85808, R64617, R70883, AA838091, AA714999, AI434513, N63149, AA632765, C14480, AI471467, AW007424, AA468196, AA558404, N95156,

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HOSGJ17	324	508870	1 - 319	15 - 333	AA430297, AI633618, and AW293117.
HOSMD84	325	959483	1 - 1036	15 - 1050	N75110, and H71506.
HOSNO86	326	858938	1 - 464	15 - 478	W19582.
HOSOE05	327	930946	1 - 494	15 - 508	AW341882, AW089950, AW392414, AA768179, AI223968, AA573000, AA429481, AI142551, AA135761, AA515172, AA568127, H86579, AW236277, AI185394, AI471455, AA626840, AA666295, AW151247, AA527109, AI687343, AA368155, AI370470, AA720582, AA507526, AA662629, AA664248, F23327, AA657910, AA225100, H01852, AA702717, AA706495, R34070, AI857366, AA480486, AA469230, AA338266, AA550959, AA829565, AI521042, AI701250, AA502110, AI709174, F23338, AA503142, AA250955, AI358501, AI590404, AI624379, T48723, AI521393, C75533, AA655037, AA469441, AW083934, AI523205, T94072, AI281943, AA484892, AL048825, AA716460, AI355103, AI431513, AI635440, AW080724, AA456937, AA377318, AA773881, AW409763, AA224525, AW404666, F34506, AI923331, AA187760, AA736447, AA714110, F27015, H85059, AI123488, AI762302, AA643434, AI114657, AA362349, AW068580, AA946848, AI821382, AI678812, AA535494, AW272389, AA548710, AI668605, AI499954, AI820534, F00688, AA610374, AI679394, AI925423, AA643424, AI369076, AI679902, AA228442, AI288033, R80563, AA483483, AA856817, W28961, T53133, AA741301, AA808725, AW150167, AA559241, T70539, AA678622, AW368401, AA601212, T07903, AA298365, AA487829, AA654464, T92803, AW162555, AI811647, AA368012, AI250019, AA598740, AW019964, AA709110, AI144055, H81700, AA481779, AI733856, T59930, AI366981, AA714073, AA074351, AA572921, AA810158, AA657835, AA468923, AA206163, T03928, AA715876, F32248, F35946, H77505, AL048060, AA664169, AA581525, R87135, AA373861, AA630845, AA487209, AA992126, AA578973, F26953, AA374525, AA568856, AI289505, AI359200, T03576, AF150410, AW157005, AI356440, AA507343, AW404647, AA458573, AI114680, AL021578, AC004673, AL034421, AC011456, U96629, AC018633, AP000503, AF134726, AL034345, AL033521, AC006101, AC002994, AL049869, AL022398, AC003966, AL109952, AC004623, AL031431, AC002400, AC004773, AF196779, AL050341, AC007068, AC002404, Z83847, AL009183, Z97876, AC005102, AL109827, AF000504, AC004849, AL080243, Z94801, AC019014, AF129756, AC004901, AC005189, AC006111, AC004895, AC004999, AC006511, Z68323, AF061032, AF003626,

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HRDAB18	328	509019	1 - 263	15 - 277	AA372168.
HRDAB60	329	509428	1 - 323	15 - 337	AA372225, AA514809, AA501943, and AC008082.
HRDAF07	330	954331	1 - 317	15 - 331	
HRDAF69	331	956269	1 - 212	15 - 226	AL022320.
HRDAF90	332	531026	1 - 311	15 - 325	AB020878.



HRDAH91	333	525525	1 - 305	15 - 319	
HRDBA76	334	534304	1 - 337	15 - 351	Z98304.
HRDBC02	335	921144	1 - 599	15 - 613	AA372229.
HRDBC30	336	530858	1 - 235	15 - 249	
HRDBC52	337	867169	1 - 299	15 - 313	
HRDBD35	338	525526	1 - 367	15 - 381	
HRDBE07	339	954289	1 - 356	15 - 370	
HRDBE18	340	956267	1 - 466	15 - 480	AA253263, AA973971, and T88817.
HRDBE19	341	534495	1 - 381	15 - 395	
HRDBE41	342	530856	1 - 370	15 - 384	AB023049, AC006138, and AP000513.
HRDBG59	343	507381	1 - 300	15 - 314	
HRDBI81	344	932761	1 - 303	15 - 317	
HRDBI28	345	925457	1 - 336	15 - 350	
HRDBK03	346	925460	1 - 356	15 - 370	AI694154, N58235, T40838, T40853, AA485402, AI521019, AI761393, AW068580, AI620266, CI5362, AI018726, AA584493, AA324088, AA326330, T47138, AA487415, AI872229, AA614647, AA487296, AA584183, AA487209, AA558404, AI953360, R94909, R84335, H94979, AA626840, AA514450, AI243793, AI538491, AI270647, AI744933, R76565, AL039761, AA167179, AL034417, AB017602, AC005697, Z93023, AL121694, AC005874, AF134471, AC007151, AC004750, AC005568, AL034555, AP000144, AC004983, AL031668, Z30952, U07561, AC004798, Z82214, AC004988, AC005206, AC008015, AL031662, AC005667, AC005288, AC005803, AC004067, AF112441, U63721, U52112, AL109628, AC001531, AC007566, AL008718, AP000555, Z98052, AL121603, AL109967, U70984, AL109623, AC003051, AC008273, AL031053, Y11493, AC007225, AC006277, AL031388, AP000689, AL033521, AC006120, X15943, AC005514, Z97876, AF141309, Z83840, AC005231, AL022330, AC007227, AC005600, AL031667, AC004478, AC005822, AC005768, AC003690, AC005316, AC005343, AL049697, AC005317, AC005406, AC005940, AC007993, AF031076, AC005775, U89337, AF031078, AF030876, AC002477, AC003665, U52111, AL096791, AC005736, AL021394, AC004149, AC005480, AF196970, AL133448, AL022401, AC004477, AC005755, AL050348, AL021578, AC005799, Z83844, AC002991, Z97635, AC004973, AL009051, AF196972, L78810, AC005146, AC005036, Z97054, AC005529, AL034420, AC002091, AL031597, AC006388, AC004953, AL031432, AC006948, AC006449, AJ003147, AC005412, AP000493, AC003036, Z93016,

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HRDBL61	347	575229	1 - 336	15 - 350		AW139046.
HRDBL75	348	524423	1 - 254	15 - 268		
HRDBM42	349	530849	1 - 361	15 - 375		
HRDBQ18	350	954274	1 - 380	15 - 394		U53331.
HRDBQ38	351	533939	1 - 310	15 - 324		AA513046.
HRDBQ64	352	879705	1 - 478	15 - 492		AL079303, AL133355, M15366, U91323, AL049569, AF217403, AF165124, AC006111, Z84488, and AC006241.
HRDBQ82	353	533947	1 - 401	15 - 415		
HRDBR04	354	927900	1 - 340	15 - 354		
HRDBR35	355	867167	1 - 303	15 - 317		
HRDBT72	356	507847	1 - 340	15 - 354		
HRDBU70	357	971700	1 - 75	15 - 89		AL049745.
HRDCA61	358	921128	1 - 442	15 - 456		
HRDCB18	359	968554	1 - 336	15 - 350		
HRDCD12	360	921796	1 - 419	15 - 433		
HRDDF49	361	867159	1 - 121	15 - 135		
HRDDF95	362	967837	1 - 434	15 - 448		
HRDDH84	363	867156	1 - 470	15 - 484		AA287503.
HRDDN54	364	932764	1 - 301	15 - 315		AC004853.
HRDDN90	365	531117	1 - 310	15 - 324		AF015262, and AJ229043.
HRDDY26	366	526783	1 - 153	15 - 167		
HRDDY73	367	574336	1 - 439	15 - 453		
HRDDZ76	368	574324	1 - 113	15 - 127		AC002210, and AC004227.
HRDEB78	369	526861	1 - 284	15 - 298		
HRDEC91	370	747169	1 - 627	15 - 641		
HRDED92	371	936045	1 - 296	15 - 310		AL139054.
HRDEG76	372	574326	1 - 310	15 - 324		
HRDEJ76	373	574335	1 - 152	15 - 166		
HRDEK44	374	574380	1 - 210	15 - 224		
HRDEL91	375	790374	1 - 204	15 - 218		T84539, AI858864, AL034553, Z85986, AC005288, L78833, AL049576, AL021707,

HRDEO12	376	867140	1 - 279	15 - 293	<p>AC007919, AL133163, AP000694, AL109799, AC005049, Y10196, AC003007, AL049839, AC005057, Z81308, AL023553, AL122020, AL049757, AC005632, U62293, AL031281, AL022163, AP000509, AC006530, AC006468, AC005253, AC006449, AL035088, AP000692, AC003663, AC004126, AC004526, AP000044, AP000112, AC005581, AP000023, AJ246003, AC005231, AC002301, AC006112, Z82178, AL031681, AC005746, AC005722, AC002431, AL121603, AC012627, AC006285, AC003101, AC007052, and AC005081.</p> <p>AA745407, T52786, AA757869, AA320095, AA779599, AA508103, AA302763, F07564, AA745388, AW440424, AA366676, AI002863, AA424249, AA112791, AA084148, AA713720, AA083850, AA993165, AA339592, AA351808, AA362440, AA508882, AA496309, AA856815, AA230075, AA347203, AA496941, AA336058, AA744063, M86139, AI940546, AA015948, AI929418, AI929460, AA454504, H27788, AA748840, AI032411, AA768079, AI701898, AA010265, AA372231, AW028376, AI345256, T31290, AI571094, AA629939, X84712, AA372389, AA383937, AA297496, AA085372, AI337065, AA349923, AA736488, AA368329, AI445338, AW407007, AA744018, AA579044, AA557727, AA364006, AW377912, AA084950, AA338216, AW157128, AA812542, H87818, AL109801, AL133243, Z98036, AC007283, AL031767, AC004895, AL035658, AL034429, AF001548, AL132777, AC004893, AC004491, AL031283, AC006509, AC007688, AL021546, AF047825, AC007157, AL035454, AC005670, AC006088, AL049830, AC002425, U07561, AC005971, M63796, AC003043, AL049538, Z83844, AC012085, AC006312, AP000501, AC004158, AC004019, AC005330, AC004985, AL022336, AC007240, AC009247, AC004967, AL021453, Z82176, AL135960, AJ131016, AC007052, AP000349, AB008681, AC006946, AC004000, AC006148, AP000032, AC006101, AC005231, AC006006, AC004223, AL022316, U62293, Z82206, AL031295, AL031589, AC008928, AF064857, AF165926, AL117258, AC005057, AF134726, AL023775, Z82244, AL035455, AC006130, AL121934, AL117391, Z84480, AL034582, AC005516, AC009501, AC002126, AC005740, AL031657, AC005015, L05367, AD001527, AC005500, AC004815, AC005081, AC000159, AL031650, AC005940, Z95152, AC007367, AL049539, AF207550, AC004520, Z95889, AC007541, AC005786, AP000047, AL109628, U02057, AC007686, AL049764, AC003690, AL022721, AC004098, AC005871, AL049760, AC006084, AC005482, AC005581, AF001549, AC006441, AL031121, AF111168, Z70281, AC005599, AP000133, AP000211, AC006141, AL021808, AP000117, AC002350, AC004820, AL121658, Z99128, AC005778, AC004526, AP000500, AC004253,</p>
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HRDE076	377	952894	1 - 606	15 - 620	AC005060, AF111170, AB020868, AC004132, AC006511, AC006965, AL133448, AC003086, AL021394, AL031311, AC002369, AC004650, AL031291, U63721, AC004922, AL049569, AL031775, AC005565, AC011594, AP000050, AL049843, AL020997, AF042089, AL050348, AC004883, AL021392, AL008719, AL035696, AL024507, AL023880, AC006071, AP000269, AC006013, AL109952, AL031005, AC007243, AL033397, AP000555, AC005512, AC004914, AP000115, AC000070, AC004707, U89336, AC002395, AL121754, AL109963, AJ011930, AL035588, AC006162, AL117329, AC006063, U47924, AB014087, AC007917, AC008101, AC004084, AL008631, AF222684, Z97630, AL035249, AL080243, U81031, AC000028, Z93244, AP000116, AF129756, AL031433, AC005049, AC006505, AL049776, AC002314, AJ246003, AL080250, AC004856, AC002094, AC008009, AL096701, AL035457, AC016027, AP000103, AL096712, AL117330, AC005793, AC004188, AC006930, AL022163, AC016830, AC005484, AC004190, AC005531, AL022398, AC005914, AC007327, AF195658, AC004832, AL050341, AL035659, AL109956, AL031577, AC002470, AF124730, AC006360, AC005695, AL135744, and AC005235.
HRDE076	377	952894	1 - 606	15 - 620	
HRDEP31	378	766222	1 - 205	15 - 219	
HRDEP75	379	574431	1 - 366	15 - 380	
HRDEQ30	380	506774	1 - 314	15 - 328	AI051942.
HRDEQ96	381	507543	1 - 446	15 - 460	AA634654.
HRDES2	382	867115	1 - 340	15 - 354	
HRDES65	383	526823	1 - 395	15 - 409	
HRDET67	384	825182	1 - 333	15 - 347	
HRDET91	385	827084	1 - 426	15 - 440	
HRDEU33	386	572905	1 - 306	15 - 320	
HRDEU42	387	881296	1 - 323	15 - 337	
HRDEU43	388	765813	1 - 146	15 - 160	N95696, AA683130, N95587, N95562, and AL021368.
HRDEU61	389	575566	1 - 405	15 - 419	
HRDEU78	390	573031	1 - 321	15 - 335	AC004031.
HRDEU93	391	844316	1 - 449	15 - 463	R97129, and Z92544.
HRDEV13	392	574442	1 - 107	15 - 121	
HRDEW02	393	848793	1 - 319	15 - 333	R69655, AA504728, AW197426, AW239197, R61016, L44427, H09430, N98902, Z42694, AA432395, and AA337216.

HRDEW30	394	526812	1 - 482	15 - 496	Z68226*
HRDEW90	395	574288	1 - 415	15 - 429	AC003077.
HRDEY14	396	574438	1 - 485	15 - 499	AC009263.
HRDEZ06	397	936072	1 - 402	15 - 416	
HRDEZ54	398	867127	1 - 461	15 - 475	
HRDEZ60	399	919386	1 - 208	15 - 222	AI949774, AA493365, AI039944, AI332543, AW082899, AW157648, AA300420, AA706469, R88367, AI969957, and AI167160.
HRDEZ64	400	536668	1 - 66	15 - 80	
HRDEZ84	401	575553	1 - 474	15 - 488	
HRDFB47	402	508001	1 - 316	15 - 330	AI932599, AA486559, AW002350, AA719531, AI345418, Z18873, AI144101, AC005332, AC007546, AC004686, AL096791, AC007773, AC005736, AL022165, U50871, AL121655, AC002350, Z69838, AC002492, AC006064, AC004526, AL049759, AC005488, AL049636, AC005531, AC006449, AC008372, AC002992, AL031680, AC007308, AC005207, AC004033, AC003689, AC004797, AC005225, AC005081, AL035420, Z98743, AL020993, AC009247, AL049569, AC006285, AP000510, AL133246, AC002400, AL031291, AL109758, AC005412, AC004382, AC005829, AL022476, AI229042, AC005632, AC006006, AC005703, AC016027, AC006581, AC016830, AL035413, AF129756, U91323, AC005324, AC005071, AC002395, AC004832, AL022326, AL049776, AC005015, D84394, AC004477, U80017, AP000086, AC002565, AL034548, AF015723, AL096701, AL049709, AC004821, AC004983, AC005037, AC005667, AP000117, AC009509, AL035683, AC007182, AC000353, U95742, AL049694, AL009183, AC007686, Z98884, Z84484, AC007216, U95090, AL049869, AC008018, AC005206, AC005104, Z97196, AL050307, AL133448, AC006121, AC006538, AC006160, AC005520, AC005924, AC004887, AC004087, AC008045, AC008119, AC004638, AC007435, AC002404, AL049539, AL133163, Z83822, AC000003, AL035086, AL117258, U07000, U93237, and AC002091.
HRDFB78	403	589478	1 - 402	15 - 416	Z78337, AW375353, U55777, T60176, AA364491, AI140371, AW393482, AW387144, AW402704, AA338532, and T30802.
HRDFC68	404	574205	1 - 384	15 - 398	Z94044.
HRDFE73	405	574142	1 - 322	15 - 336	
HRDFE74	406	765750	1 - 301	15 - 315	AI452477, AA526633, AC006211, AL031276, AC004893, AL096712, AC000025, AC003687, AL109760, and AC003101.
HRDFE42	407	953913	1 - 78	15 - 92	

HRDFE62	408	574436	1 - 508	15 - 522	T77462.
HRDFG25	409	574433	1 - 332	15 - 346	
HRDFG37	410	792517	1 - 280	15 - 294	
HRDFG46	411	574439	1 - 365	15 - 379	
HRDFH14	412	575578	1 - 149	15 - 163	
HRDFH24	413	575245	1 - 423	15 - 437	<p>AI284640, W00807, AI291124, R97934, AI471481, AI282832, AA862173, AI245679, AA947811, AA362349, AA507547, AW265009, AI801600, AI889781, AI357551, AA515224, AI439210, AA806796, AA828704, AA810370, AA348929, AA775940, AW339568, F34498, AA557686, M86143, T07451, T05101, AA654771, AI457397, AA593247, AI866908, AA584201, AA513293, AI358571, AI291268, AI281697, AA678436, AA578861, AA213741, AA493708, AI298710, AA661948, H86305, AA669840, AW089322, AA513141, AI049634, AA831375, AI564185, . AA554319, AI364809, AA525824, AI500454, H51714, AA259245, AA713891, AA491284, AI561255, AI046409, AA610611, AW327868, AW338086, AA603156, AW103758, AI358343, AI499938, AA579075, AA348017, AA649722, AA346458, AA492166, AA847985, AA908468, N25296, AL042853, T41242, AI904894, AW265385, AA244357, AA502103, AA649542, AA649484, AA503283, AW168342, AW193609, AI859251, F33121, AI888008, AA665330, AA426277, AW265699, AI358501, AA630925, F04987, AA503284, AA225246, AI475569, AA916371, D83989, M87919, X75335, S70707, U67827, U67829, M37547, AF077058, M37551, X55923, AB023052, AC006203, AP000513, M87925, U14706, AC002536, Z94721, AC002301, U73024, AC004821, AL031736, AF015151, AC006138, AL031685, Y10196, AC005324, U14716, AF015156, U14713, AL133245, AL022238, AL096707, AC005622, AC006292, AL035681, AC016830, AF018071, D87675, DI3624, AC007731, AL109984, AL078613, M19045, J03801, E01888, E02193, AL022727, AC006449, AC006004, AL122003, AC002380, AP000141, AC004388, AC007546, AB020863, S43650, AC007050, AC004263, AC005261, U07562, AL132987, AC006274, AL021368, AC010175, L49046, Z68223, AR047856, AC004687, AP001172, AF042090, AC004076, AC007064, AC007363, AF129756, AC005900, AC005280, AC006057, AC008039, AC005682, AC008124, AP000326, AP000353, AL021937, AC004853, AC002059, AL121934, AL022067, AC004151, AP000054, AP000169, AP000359, AC000067, AC000590, Z68192, AL021154, AC002480, Z69917, AL110172, AC002073, AL031729, AL022237, S75337, U14695, AC006959, AC004858, AC000120, U14710, AL023656, AL117352, AC004408, AL031281, AC005771, AC003688, AC002070, AL133371, AC006352, AL008709,</p>

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HRDFH25	414	953882	1 - 370	15 - 384	
HRDFH39	415	574558	1 - 364	15 - 378	
HRDFH77	416	953673	1 - 422	15 - 436	
HRDFI13	417	574561	1 - 363	15 - 377	
HRDFJ71	418	574553	1 - 406	15 - 420	
HRDFK03	419	924925	1 - 464	15 - 478	
HRDFK41	420	867106	1 - 315	15 - 329	AW410890, AL079806, and AB007931. AI002928, AA804808, N55076, AA018258, AA804694, AC004983, AC004775, AC005225, AC005519, AL096791, AL031680, AC005291, AL022311, AC003072, AC004383, Z98949, AC006285, AL031602, AL021579, AL031985, AC005399, AP000113, AP000045, AL109623, Z84469, AC005755, AC007421, AC002395, AL022316, AP000555, AC002477, AF045555, Z94801, U66532, Z97056, AC007021, AL096701, AC005914, U95741, AL022238, AL049759, AC005696, AC005666, AC007225, AC004884, AF109907, AC016025, Y11107, AL008710, M26434, U47924, AC006388, Y14768, AP001054, AC005081, AF064861, AC005218, AF001548, AC009225, AC005730, AC006367, AC006101, AC005940, AC009509, AC005632, AL008718, AC004975, AC007283, and AC006362.
HRDFM18	421	574435	1 - 108	15 - 122	
HRDFN95	422	574565	1 - 116	15 - 130	
HRDFQ64	423	733847	1 - 256	15 - 270	AA832055, AA077542, AA770651, AC004987, and AL133216.
HRDFQ75	424	525524	1 - 240	15 - 254	AL132987.
HRDFT06	425	867109	1 - 389	15 - 403	
HRDFT15	426	574549	1 - 415	15 - 429	
HRDFT45	427	506584	1 - 530	15 - 544	AC004142.
HRDFT84	428	584823	1 - 445	15 - 459	AA309894, AB009022, AB012143, AB012142, AF025654, AF034568, AF025653, AB009023, and AB009024.
HRDFU48	429	573030	1 - 301	15 - 315	

HSAX53	430	518795	1 - 302	15 - 316	
HSB66	431	523348	1 - 323	15 - 337	
HSBV67	432	529483	1 - 308	15 - 322	AC007536, and Z97832.
HSHCF34	433	529313	1 - 214	15 - 228	AL035415.
HSKCS36	434	529163	1 - 233	15 - 247	
HSKCT33	435	866514	1 - 297	15 - 311	
HSKDA70	436	757183	1 - 599	15 - 613	W49690, AA284238, W49689, AI950805, AI085909, AI457351, AI866940, AW013806, AI246901, AW051765, AI739482, AA394133, AI380566, AI921768, AI827273, AI860590, AW009629, AI768051, AI392972, W45591, W45590, AI022944, and AB017614.
HSKDJ16	437	661928	1 - 330	15 - 344	AL049464.
HSKEF43	438	866410	1 - 301	15 - 315	
HSKEK63	439	744336	1 - 376	15 - 390	AA372904, C16438, AW380254, AW168420, AA534258, AI674174, AA372949, T39494, AC005331, AC006013, AL022311, AC004827, Z99570, AL020997, AJ010770, Z93023, AC005746, AP000505, AC006007, AC007546, Z75741, AC002563, AL024498, AL021546, AC007845, AC002398, Z94722, AC004815, AC004703, AL133404, AC004526, Y14768, AC005482, AC005200, AC005039, AC002319, AL021451, AC004099, AC004884, AC008119, AC005324, Z95152, M29929, AC007877, AC006112, AF129756, AC003101, AF107885, AL031320, U82828, AF007136, AC004976, Z69666, AL031668, AC004953, AC006965, AF196779, AF064751, AC005355, AC004702, Z81314, AC002541, Z69388, U91318, I47234, AC008273, AP000690, AC004152, AF002997, AL031117, AC009784, AF111169, AC004106, AL109628, AC004148, AC004253, U07562, and AP000318.
HSKEM02	440	969071	1 - 426	15 - 440	AA143157, AA063324, N57369, W81341, and AL133355.
HSKET11	441	967000	1 - 414	15 - 428	
HSKHJ11	442	965002	1 - 433	15 - 447	Z98046.
HSKHS71	443	911592	1 - 367	15 - 381	
HSKIT38	444	855173	1 - 369	15 - 383	
HSKJS05	445	930979	1 - 64	15 - 78	AA731590.
HSKKD70	446	916984	1 - 563	15 - 577	
HSKKL06	447	934040	1 - 646	15 - 660	
HSKNO53	448	728210	1 - 521	15 - 535	AW275953.
HSKWA56	449	916496	1 - 423	15 - 437	
HSKWA78	450	731756	1 - 516	15 - 530	



HSKWA79	451	733394	1 - 488	15 - 502	W90331, AA398850, and AA435854.
HSKXG06	452	935455	1 - 312	15 - 326	
HSKXJ15	453	866373	1 - 437	15 - 451	AL117340.
HSKXN20	454	668928	1 - 290	15 - 304	AI610572, AA494027, AW089962, AW020620, AW021195, AP000703, Y10196, AC004079, AL080243, AP000702, AC005067, AC005874, AF134471, AC006453, AL031255, AL031733, AL049767, AC007450, AC005089, Z83836, U95090, AP000347, AC005803, AP000352, AC002381, Z98048, AL033397, AC005777, AC005265, AC005696, Z98200, AL024507, and AC002117.
HSKXPS8	455	955073	1 - 352	15 - 366	AA372956, AL031737, AP000553, AC004491, Z83826, AL050318, L78810, AC005484, AC007685, AL078602, AC005667, AC007298, AF049895, AC004699, and AC005206.
HSKXQ58	456	736045	1 - 376	15 - 390	AI810143, AI799021, AI347650, AW020141, AA143516, AA551503, H56729, N29948, N54304, AA601919, AA079101, AW089810, H79394, AW402170, AI580898, AL031257, AL022719, AL021808, AC008123, AC003007, AC005632, D86864, AC005776, AC005539, AC005262, AL022315, AP000126, AP000204, AC005252, AP000556, AP000244, AP000557, AC007050, AC007308, X89398, AL031280, AC007637, AF087913, AC005251, AP000150, AP000009, AC006016, D28877, AC005071, AC004019, AC006137, AL031386, and AC003684.
HSKYG66	457	698007	1 - 333	15 - 347	AI209100.
HSKYH52	458	466574	1 - 419	15 - 433	
HSKYJ96	459	921032	1 - 346	15 - 360	
HSKZE12	460	970639	1 - 104	15 - 118	
HSKZE32	461	959400	1 - 273	15 - 287	
HSLAB77	462	772652	1 - 301	15 - 315	AA464651, H60107, AA419210, R11432, AW151815, and AC006254.
HSLBO30	463	574086	1 - 198	15 - 212	AC007392.
HSLBW19	464	671738	1 - 212	15 - 226	
HSLBX08	465	959911	1 - 257	15 - 271	Z95152.
HSLBX20	466	574004	1 - 422	15 - 436	AC005922.
HSLBZ91	467	573987	1 - 281	15 - 295	
HSLCB15	468	693455	1 - 619	15 - 633	H24866, AA031368, W47079, W46779, H84840, N30984, W32033, AA018530, H26464, N40269, AA459816, AA296636, AI751106, W19406, R24391, R21973, AA370945, AW366386, AA374691, N40640, H39859, AA296525, AA446165, AW377667, AA322178, AI366199, N28622, AW367978, AA382270, T85743, AA337106, AI684270, AW367975, R57416, Z92846, and AF125535.

HSLC146	469	529622	1 - 265	15 - 279	AL096677.
HSLC147	470	908627	1 - 352	15 - 366	
HSLC138	471	951028	1 - 232	15 - 246	
HSLCP75	472	529631	1 - 340	15 - 354	E08867.
HSLCV95	473	793080	1 - 315	15 - 329	
HSLDA25	474	679301	1 - 370	15 - 384	
HSLDB29	475	866340	1 - 424	15 - 438	
HSLDC06	476	936010	1 - 259	15 - 273	AI672480..
HSLDG13	477	913664	1 - 325	15 - 339	
HSLDI16	478	574014	1 - 202	15 - 216	
HSLDI24	479	574050	1 - 349	15 - 363	I09483, I09484, and I09485.
HSLDI94	480	753657	1 - 447	15 - 461	
HSLDK43	481	675440	1 - 521	15 - 535	
HSLDM32	482	699486	1 - 299	15 - 313	
HSLDM79	483	526740	1 - 335	15 - 349	
HSLDP16	484	573210	1 - 433	15 - 447	
HSLDW65	485	689722	1 - 416	15 - 430	
HSLBE25	486	669654	1 - 389	15 - 403	
HSLC25	487	572859	1 - 400	15 - 414	
HSLC36	488	936003	1 - 365	15 - 379	
HSLD38	489	709381	1 - 506	15 - 520	
HSLD42	490	572860	1 - 375	15 - 389	
HSLDE46	491	572878	1 - 322	15 - 336	
HSLF89	492	572883	1 - 346	15 - 360	
HSLG74	493	825500	1 - 385	15 - 399	AI526055.
HSLH57	494	584090	1 - 130	15 - 144	F07221, AA307815, N99978, AI660617, AI906507, AW166174, W30916, AA877685, AI692837, and AA434201.
HSLJ22	495	572863	1 - 304	15 - 318	
HSLK46	496	573212	1 - 275	15 - 289	
HSLK070	497	841952	1 - 354	15 - 368	AL048938, AW385766, AA417805, AA134623, AW239566, AA075905, AA167826, AA134649, AA375645, AW005427, and AI424382.
HSLFE34	498	706986	1 - 396	15 - 410	
HSLFF91	499	572885	1 - 413	15 - 427	AI095822, AI827514, AA909148, AI635994, AI339613, AI242071, and AI343397.
HSLFM86	500	785489	1 - 427	15 - 441	

HSLFS42	501	948740	1 - 287	15 - 301	
HSLFS45	502	717782	1 - 360	15 - 374	
HSLFT76	503	725788	1 - 382	15 - 396	
HSLFT89	504	786061	1 - 378	15 - 392	
HSLFU01	505	916448	1 - 404	15 - 418	
HSLGD23	506	675872	1 - 436	15 - 450	
HSLGH26	507	681705	1 - 426	15 - 440	
HSLGK79	508	774049	1 - 377	15 - 391	
HSLGV91	509	780005	1 - 428	15 - 442	
HSLGX20	510	669648	1 - 424	15 - 438	
HSLHA55	511	866273	1 - 392	15 - 406	AI699746, AI869424, AA484365, AA015948, AA788575, AI003051, AA598608, AA814719, AA463832, AA243128, AI798714, AA015753, AW148821, AI002786, AI383589, W21030, AA665411, AI000381, AI445699, AA846014, AA493245, AI791664, AA455804, AI702049, AI138262, AW192930, AI734158, AA455202, AL121039, AI734193, AW410844, AI064968, AA653228, D25266, AL038971, AA584738, AI167784, AA226133, AI800445, AA300049, AI016729, AW265468, AW085626, Z97206, AL022147, Z97181, AC007842, Z84480, AF053356, AF006501, AL031622, Z97056, AL031587, AL031117, AC007371, AL109628, AL024507, AC005399, AC005409, U82672, AC005565, AC007151, AC007676, AC004914, Z86090, X69907, D87008, AC000040, AJ250235, AC004663, D88268, AL096757, Z83851, AC005914, AC007690, AC007541, AL117329, AC005375, AC004067, AC005531, AC006198, AC005772, AC008040, AF053139, M94634, AC005368, AF111169, AC005345, AC000387, AC006006, I47222, AC006261, AC005808, AL035079, AC004020, AC002456, AL121595, AC005391, AC005379, AL035400, AL021937, AC004785, AJ010598, AC006285, AC009336, AL050333, AC004815, AF064865, AC004832, AC005060, D83402, Z69650, AF000227, AC002120, Z49918, Z68277, AC005256, AC006138, Z15025, AC002106, AC007565, AC005214, AC007536, AL022144, AF038458, AF190465, AP000087, AP000513, AL008731, AL020993, AC005033, AC007899, AC005277, AF064866, AB023049, Z98950, AC006509, AP000689, AC005844, AL021578, AL031311, and AL079342.
HSLHC22	512	673918	1 - 440	15 - 454	R64409.
HSLHP20	513	669210	1 - 418	15 - 432	
HSLIA21	514	668116	1 - 388	15 - 402	

HSLIG54	515	713982	1 - 382	15 - 396	
HSLIJ61	516	918071	1 - 458	15 - 472	W19840, R50853, AA482385, T72743, H21057, T72748, R10320, and W01711.
HSLIJ57	517	659533	1 - 377	15 - 391	
HSLJB11	518	966227	1 - 131	15 - 145	Z83844.
HSLJJ21	519	670330	1 - 329	15 - 343	A40155, and A40156.
HSLJJ83	520	727874	1 - 295	15 - 309	AC007193.
HSLJK88	521	923108	1 - 203	15 - 217	AI914865, AW377768, AA767396, AA975495, AA972715, AI991550, AL132776, and AB018319.
HSLJN31	522	750394	1 - 337	15 - 351	
HSLJN49	523	920062	1 - 448	15 - 462	
HSLJN61	524	966267	1 - 485	15 - 499	AI014258, and D89677.
HSLJN71	525	759941	1 - 335	15 - 349	
HSLJQ31	526	961447	1 - 427	15 - 441	H02450, R32623, AA349144, R11455, R27382, AA599094, N31153, N25174, N35733, H12488, AA082514, W60949, R06834, N26982, H04870, AW361043, and AB020685.
HSLJW53	527	866261	1 - 240	15 - 254	AA872180, AW304637, AI927741, R14941, T80162, AA702988, AA226346, AA134007, AI216978, AI358513, AA634227, AI151261, AI826253, AA662431, AA766883, AW028950, AA838162, AA297145, AA706845, T87973, AC006211, AL078639, AP001137, AP000325, AP000168, AP000054, AP000122, AC006344, AF196969, AL080239, AF110527, L78833, AC004876, AD000092, AL117330, AC004859, AL022476, AC004833, AC005476, Z83840, AC006441, AC006581, Z58851, AC005233, AC004057, AL035398, AC002365, AC003046, AC007371, AC007537, AL049776, AL022318, AC007868, AC005089, AC002400, AC007551, AC002470, AC007308, AF141325, AL121593, AC007377, M55523, AC004522, AC004817, AC007263, AC008498, AC005914, AL034420, AC004858, AC002476, AF109907, and D87675.
HSLKC70	528	866256	1 - 410	15 - 424	
HSRAX95	529	747078	1 - 311	15 - 325	Z68164.
HSRBE02	530	921205	1 - 341	15 - 355	W79904, R73478, H42289, and AL137459.
HSRDE58	531	519542	1 - 208	15 - 222	AC000378.
HSRDI39	532	921749	1 - 381	15 - 395	AL117454.
HSRDI68	533	530333	1 - 244	15 - 258	AL080190.
HSRDK92	534	838033	1 - 209	15 - 223	AF095719.
HSRDL32	535	530294	1 - 261	15 - 275	AL045354.

HSRDM42	536	523843	1 - 136	15 - 150	
HSRDN23	537	530334	1 - 200	15 - 214	AC005703.
HSRDQ89	538	780221	1 - 178	15 - 192	
HSRDS77	539	530289	1 - 230	15 - 244	AC000026, and AC002059.
HSREB43	540	524678	1 - 272	15 - 286	
HSREC27	541	753810	1 - 296	15 - 310	
HSRED45	542	530233	1 - 327	15 - 341	
HSREG25	543	523815	1 - 347	15 - 361	
HSREG40	544	712779	1 - 534	15 - 548	AI032560, AI040579, AI040370, AA702902, and AI685149.
HSREG49	545	723267	1 - 206	15 - 220	
HSRFC96	546	558385	1 - 279	15 - 293	AL109852, Z93403, AL035468, Z95124, AC008041, AL035552, AL135783, AC007736, and AL008709.
HSRFD34	547	575288	1 - 139	15 - 153	AA088873, AI079088, AI160732, AI381253, AW162324, AI992192, AI358948, AI933299, Z92910, AR036572, U91328, AC005393, AL035462, AC004890, AC005366, AC002509, AC007227, and AC010200.
HSRFD47	548	973782	1 - 428	15 - 442	AC004386, AC002418, and Z83843.
HSRFE58	549	556519	1 - 334	15 - 348	AC007198, and AC005280.
HSRFF03	550	925369	1 - 130	15 - 144	
HSRFG30	551	920265	1 - 286	15 - 300	
HSRFR21	552	529767	1 - 229	15 - 243	
HSRFZ71	553	557976	1 - 304	15 - 318	
HSRGA32	554	529726	1 - 306	15 - 320	AW192199, AL133312, AC005683, and AF172277.
HSRGB23	555	974538	1 - 413	15 - 427	AI207415.
HSRGE47	556	974539	1 - 327	15 - 341	
HSRGG66	557	556518	1 - 169	15 - 183	AC007198, and AC005280.
HSRGK48	558	535012	1 - 110	15 - 124	AA373481, and AL134562.
HSRGQ30	559	534479	1 - 407	15 - 421	AI493261.
HSRGS08	560	960211	1 - 299	15 - 313	
HSRGV79	561	921005	1 - 356	15 - 370	
HSRGW30	562	529624	1 - 296	15 - 310	
HSRGGZ32	563	699561	1 - 348	15 - 362	AI963683, and AI742748.
HSRHA45	564	974551	1 - 391	15 - 405	AL049871.
HSSAB47	565	720685	1 - 337	15 - 351	AA377682.
HSSAF46	566	508117	1 - 341	15 - 355	

HSSAN96	567	936108	1 - 239	15 - 253	AA378117, AL048143, and AA378114.
HSSAP44	568	508831	1 - 374	15 - 388	AA378135, and AA378220.
HSSAV18	569	508832	1 - 186	15 - 200	AA378151.
HSSAV88	570	508829	1 - 375	15 - 389	
HSSBO48	571	871217	1 - 357	15 - 371	
HSSBO59	572	707683	1 - 396	15 - 410	AA632960, H82330, R13151, AA528455, AL045709, AA657416, AA658320, AI150670, AA721615, AA077776, AI564508, AA652057, AA640979, F17700, AW407919, AA437402, AA487542, AA302732, AA516207, D58782, AA298387, AA125788, AA482896, F37052, AA775049, AA581914, AI446474, AI284595, AI014378, AI888405, T47460, AA362395, AA298386, AA743137, AA491484, AA809189, AI862716, AA483655, AW271904, AI679713, AA878140, AA569187, AI292236, AA663306, AW265654, AA720732, AA642053, N69462, AA165462, AL119025, AA448838, AI628224, AI493264, N45421, H55894, AA572960, H65439, AA371409, T48872, AA365744, AI524540, AW075979, AW103383, AA599495, AI473701, AI279759, AI471572, AA425922, AI627581, AA558344, AW440633, AI540107, AI803827, T03203, AA443426, AI609223, AA577732, AI460390, AW339622, AI754291, H65440, AW268277, AA493885, F26719, AI251111, AI184226, AW407340, AI114752, N38789, AA747472, AA848143, AL120976, AW117976, AA100884, AA654627, AA704643, AL037910, AW021917, AA127916, AW189353, AA507991, AI597832, AA283083, AI634323, H94289, AL041083, F33511, AI863399, AA167741, AA468051, AA228283, AA745560, AI832000, AI689019, F37223, AA632845, AA501418, AW192330, AI978792, R23352, AA831388, AA968509, AA192695, AI623563, AI270476, AI872503, AA311071, AW167154, AI253797, T94094, AW079809, AI859834, AA516225, R26134, AA515937, D56402, AW419081, AI473684, AA655005, AI754037, AI114477, AA569202, AA626829, AA467988, AI366982, AA558003, R32200, AI042342, H53562, AA579278, C06137, AI859280, AI889921, Z96050, AC004201, AC009510, Z82176, U97046, Z96568, AL109798, AL020990, Z95331, AC004902, AL033527, AC003991, AC006239, AC003042, AL023806, AC006450, AC006363, AC002065, AL121603, AL008710, AL079339, AL035454, AC005378, AL080286, AC005180, AC006372, AC005037, AF043105, AL022397, AC006006, AC005546, AC007358, AC002381, AC004643, AL024509, Z98743, M63543, M63544, AC006578, AC003098, AC006251, AC000083, U89337, AF059675, AP000500, U73167, U90094, Z73420, AL009031, Z84484, AC002326, AL009029, AC005011, AJ003147, AL031003, Z84469, AC005562, AF020503, M87918, AL021397, AC003101,

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HSSCC04	573	928001	1 - 119	15 - 133	
HSSDI02	574	871226	1 - 348	15 - 362	AL035681, Z93241, AL049839, Z82189, and AP000553.
HSSDL20	575	667599	1 - 159	15 - 173	AF084557, AC003025, AF139813, and AC004228.
HSSDL94	576	526758	1 - 285	15 - 299	D80188, AI525912, AA514184, and AR008278.
HSSDR63	577	537329	1 - 213	15 - 227	AC006071.
HSSDX20	578	783128	1 - 113	15 - 127	
HSSDX56	579	625572	1 - 358	15 - 372	AA346009.
HSSEF29	580	689837	1 - 389	15 - 403	
HSSEK75	581	766507	1 - 166	15 - 180	
HSSEU91	582	766573	1 - 163	15 - 177	

HSSEU93	583	911261	1 - 358	15 - 372			AI961823, AW166279, Y17108, and Z92544.
HSSEV89	584	572851	1 - 296	15 - 310			
HSSFF80	585	753589	1 - 285	15 - 299			
HSSFO43	586	715318	1 - 405	15 - 419			AC007367.
HSSFR41	587	707006	1 - 346	15 - 360			
HSSFX54	588	708845	1 - 429	15 - 443			T71424, R18371, and Z43782.
HSSGC65	589	955064	1 - 391	15 - 405			AI982519, AL042376, AL042377, AI361890, AI200168, AI656939, AC000385, AF061779, AC004923, and U73627.
HSSGC66	590	319740	1 - 231	15 - 245			
HSSGC72	591	760648	1 - 141	15 - 155			
HSSGD37	592	739505	1 - 308	15 - 322			AL049569.
HSSGH47	593	720367	1 - 355	15 - 369			
HSSGI20	594	668919	1 - 328	15 - 342			Z81364.
HSSGI75	595	767325	1 - 333	15 - 347			
HSSGI91	596	789411	1 - 338	15 - 352			AP000348, and AP000347.
HSSGK96	597	960636	1 - 378	15 - 392			AA378503.
HSSGL55	598	766115	1 - 599	15 - 613			W74502, AA602391, AI420864, AW249723, AW166500, AA076659, AA947286, AW148931, AA523509, N59225, C14268, AI367349, AI421445, AI936982, AI769470, AI368200, AI419527, N98776, AI684498, AI572122, AW206959, AI634762, W49625, N34422, AI217398, W31030, AA725340, AI081813, AW373882, AI672387, AA641497, AI337000, AA478173, AI766926, AI365401, AI813446, AI608807, AI382536, AI950175, AI382559, AA827390, AW183593, AI420810, AA309806, AI565511, AI362447, AA478017, AA773507, T11147, C14269, AI738446, AI800023, AI242987, AA639592, AI399691, AA659150, AA371822, AI243140, AA631086, AI659508, AI927588, AI651868, AI699620, AA335673, AI805041, AA336127, W48799, AA335414, N76692, AI916893, AI468167, AA335239, AW206563, AI873196, AW137813, AW451053, AW137008, AI823968, HI6597, AW006577, AW006554, N71461, AI401174, W79098, D19946, and AI541353.
HSSGL78	599	788924	1 - 376	15 - 390			R83708, AA515728, D44639, AL041894, AI038842, AA515138, AI762528, AA158759, AA452887, AI421257, AA581247, AA516320, AI792529, AA502991, AA630535, C14858, AI801701, H70108, AA182731, AI054193, AA773098, AC005841, AC005071, AF001550, AC007536, AL133448, AC007041, AL020997, U95739, AL034429, AL096701, AC005005, AC006597, AC002126, AL008635,



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HSSGM62	600	707685	1 - 397	15 - 411	
HSSGN47	601	707003	1 - 324	15 - 338	AI076644, AI951987, AA969026, AD000671, AF186605, and AJ007041.
HSSHA92	602	792714	1 - 396	15 - 410	
HSSJN44	603	716573	1 - 428	15 - 442	AL139054.
HSSJN49	604	708841	1 - 331	15 - 345	

HSSJU66	605	653212	1 - 248	15 - 262	AW241370.
HSSIV60	606	970749	1 - 417	15 - 431	AA972086, and AW241953.
HSSKB40	607	711130	1 - 558	15 - 572	R78078, AI672012, AI291253, AW438453, Z83844, AI139054, AI008715, Z85996, AI035072, AI035695, AF218772, AC006056, AC006508, AF037046, AF146793, AF034692, AI118503, U31796, AF019657, AC006584, AF092084, and U31316.
HSSMT78	608	712468	1 - 481	15 - 495	AA378685, AA378686, AP001101, and AC004837.
HYBAE74	609	925074	1 - 314	15 - 328	AC006121.
HYBAG11	610	967880	1 - 194	15 - 208	
HYBAU83	611	732419	1 - 226	15 - 240	AA371642, AA345063, N87410, AI886060, AI886365, AA528441, AA652329, AI743721, AA987962, AA364488, AI954525, F13749, AA626829, AI135643, AW075915, AI982634, AI751162, AW162288, AI696793, N54179, AI610603, AA360260, AA258848, AI240339, F32893, AW341903, AI216998, AI370270, AI348302, AI024782, AW402145, AW157005, AI028510, AA968509, AI270524, AW157492, AI797901, AI653905, AI634691, AI797892, AA372881, AI678785, AI471418, AI345657, AI349966, AI879394, AI796594, AI345717, AA772016, AA507837, AI039187, AI467877, AA992126, AW088843, AA215335, AI332666, AI799303, AI038909, AA364315, H78031, AA367555, AI753365, AA617954, AW300776, AA843450, AA226584, AA319813, AI244758, AA657835, AA318652, N54764, AA192330, AA206807, AA364330, AI053981, AI051037, H79308, F33121, AW271904, AA347040, AI240891, AI719644, AI921541, AA984191, AI079423, AI144094, U73167, U90094, Z84469, AI034420, AI031296, AI050307, AC007688, Z82097, AC006211, AC004263, AC006441, AC004660, AC004921, AC006241, AC005971, AI008635, U80017, AI035089, AC007199, AP000697, AC009501, U78027, AC005209, AC007055, AC000353, AP000503, AI035422, AB008681, AC006084, AC007486, AC003684, AF134726, U80459, AC004235, AC004382, AI022336, U62293, AC005664, AC005071, AC005214, AI117694, AI121655, U85195, AC005529, AC000097, AC005856, Z86090, AP000500, AC003101, AC002470, AC006547, AC005940, AC006480, AE000658, AC005772, AC005057, AI022163, AC007283, AI121769, L78833, AC007842, AC006509, AI021808, AP000248, AC004678, AC005988, AI031774, X74984, AC005922, Z98744, AI079333, AF129756, AC007038, AC006449, AI022328, AC005086, AF045555, AI049795, AI117258, AI008582, AI031447, AI022578, AI078477, Z85986, AC008040, AC005844, AC006387, AC004236, AC004129, Z94057, AP000505, Z94056, AP000556, AC000557, AC004685, AC001231, AC007041, AC005696, AC005913, Z97056, Z93241, AC000070, Z83822, AC002073, AI133245,

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HYBAX25	612	456251	1 - 341	15 - 355	T55280, Y17457, AL031133, AC005089, AC005412, AC005886, AC004472, and AC006509.
HYBAY40	613	531202	1 - 284	15 - 298	
HYBBB24	614	584989	1 - 307	15 - 321	AA806538, AI005244, and AA535437.
HYBBI18	615	584991	1 - 340	15 - 354	Z98880.
HYBBJ30	616	693345	1 - 228	15 - 242	AB032972.
HYBBL17	617	691328	1 - 232	15 - 246	AA046858, AI078144, AA022643, AI809791, N57180, AW170191, AA328923, AA401814, H27580, AI869993, AA249586, AA576955, and W67605.
HYBBK83	618	505138	1 - 595	15 - 609	AI923052, AW265688, AI862716, AA557911, AI358712, AI932871, AI380617, AW408767, AA533054, AA488687, AL039187, R92658, AW085758, AA528516, T05118, AI246796, AW268329, AI696955, AA599080, AA828834, AW023975, AA604751, AI357823, AI689198, AI821382, AA115865, AA469327, AL049576, AC002477, AC006157, AC007283, AC005089, Z98044, AL133448, AF064861, AC006071, Z82244, AC006511, AC004913, L44140, AL031589, AB003151, AC005399, Z93241, AC007707, AC007227, AC012627, AC005696, AC004254, AF134726, AC006312, U95740, Z98752, AC004967, AC004673, AC005409, AL030996, V00596, Z98200, AL049709, AC005028, AC002470, AC006057, AP000295, AC002352, AC005972, M17262, AC005288, AC005821, AC004878, AP000689, AC005519, AF111167, AC004990, AC006241, AC004242, AC002288, AC005907, AC004975, AC004933, AC005902, AC002558, AC005488, Z98036, AC005274, AC005067, AC004477, AC005379, AC007993, AC002997, AC007226,

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HYBBG93	619	531201	1 - 60	15 - 74	AF024533, and AC005088.
HYBAY92	620	792923	1 - 426	15 - 440	W01795, and N99837.
HYBAW0 3	621	925068	1 - 323	15 - 337	AA435790.
HYBAH65	622	518736	1 - 592	15 - 606	H48087, T70307, W72466, H80227, H81398, T78885, AA704555, H73669, T78410, and A W236543.
HYBAG53	623	669602	1 - 463	15 - 477	H71386, A W408254, H81132, H44291, N21071, AL801120, N36421, AW341639, AA878376, C02991, AL758487, and AA280550.
HYBAF63	624	745585	1 - 649	15 - 663	N48536.
HSSMZ93	625	530752	1 - 346	15 - 360	AA378965, AA378966, and AL035696.

HSSMZ01	626	921800	1 - 401	15 - 415	AA378938, H90844, T57767, AA824453, AA492105, AI752358, AA458452, AI783911, AA723299, AA812684, AA728973, N67313, AA167489, AA483771, AA664604, AI241831, U63721, AC005071, AL049692, AC006312, AC004878, AC005229, AC002996, AC005520, AC002544, AL031670, AC005874, AF134471, AC004099, AL109984, Z95115, AF134726, AC004263, AC004983, AC004686, AF111167, AF095703, AP000692, U80017, U91326, AC007686, AL135783, AL031666, AC004475, AC005207, AC004217, AC004996, AC007563, AC006441, AL096791, AL022322, AL021154, AL035414, AC005821, AC006026, AC006960, U62293, Z83844, AC007450, AL024498, AC004520, AC004659, AL080243, AC006512, AP000356, AL049552, AP000505, AC006211, Z98051, AC004019, AC000003, AC006101, AL049745, Y14768, AC004132, AC016027, AC005031, AC004814, AC002045, AF129756, AC004938, AC005740, AC006111, AL033521, AL009181, AL008726, AC006237, AP000280, AC006450, AC005971, AC007344, AC007227, AC000025, Z83826, AC004491, AP000248, AC004883, AC002316, AC008064, AL035422, AP000503, AF109907, AP000107, AC005972, AC000026, AL049636, AC006487, AL109798, AL022316, AC005829, AC004386, AC005668, AC007376, AL049869, Z68756, AC005696, AP000552, AC016830, AC005057, AL023553, AL023913, AF190465, AP001054, AP000030, AP000133, AP000211, AF200465, AC005922, AC008498, AL031311, AL133243, AL117355, AC005369, AL022336, AC006511, AC002400, AC005914, AC008372, AF003626, Z95114, AL031390, AF196779, AL079304, AC004383, AL021579, AC007308, AC005702, AC009891, AP000228, AL133246, AC004125, AC004966, AC003110, AC002565, U78027, AC004453, AC006057, AL022323, AL021939, AP000035, AP000104, AC002472, AC007277, AL023653, AC003664, AC006040, AF111168, AC007546, AL132987, AP000557, AL020989, AL049776, Z93930, AP000497, AP000140, AC003667, AC006530, AL049653, AC007073, Z99716, AC005803, AC004032, AC004458, AP000696, AC008018, AF152364, AL133163, AC008062, AC005837, AC002288, AC007151, AC006254, AC006362, AC004967, Z93241, AC006480, AC004815, AC005412, AC005011, Z93017, AL023807, AL109628, AF024533, AL021393, AC004808, AC004583, AC007226, AC007540, AC005538, AC004655, AC000393, AL049569, AC005553, AC004663, AL049712, AL031729, and AL031005.
HSSMW90	627	975081	1 - 306	15 - 320	AA378852, AI149537, AW130188, AW173759, AA715418, AI280504, AW149288, AA489978, AL035413, AL050332, AB014078, AP000514, Z98749, AC006139, AC002468, AC008064, AC005589, Z80901, AL109753, AP000215, AP000128,

HSSMT76	628	928421	1 - 299	15 - 313	<p>AP000206, AP000245, AP001056, and AC008163.</p> <p>AA378683, N72524, AA378682, N57752, N53565, AA831903, AI017251, AW103030, N91572, AI689198, AA655005, AA716348, AI580898, AA077667, AW341903, AI336480, AA340747, AW002831, AA347114, C05986, AI457397, AA533033, AI866908, AI027056, N75391, AA071334, AW151247, AA599352, AI244356, AA086318, AA657416, AA664604, W47183, AI753365, AI824541, AI499376, AI500552, AA630535, AA347034, W79504, AI471481, AI537955, AA773463, T57267, AA603911, N32878, AI291268, AA086344, AA167659, AA644551, AI291124, AI745325, AA488620, AA300391, AA303054, AA613138, AA491814, R64617, AA832145, AI801563, AA665021, AA284184, AW277174, AI291037, AA568778, AA828637, AI267269, AW270768, AI446205, AA502991, AW157005, AA573213, AW438616, AI080618, AW276827, AW193432, AI339845, AA916600, AA483771, AI270476, AA362349, AA551503, AA577906, AA446616, AA350859, AI688846, AA599920, AA553363, H90844, AA579184, N25296, AI687206, AA381138, C15092, AA367986, AA437161, AL041706, AA579736, N22797, F01666, AI350211, AA992126, AI580652, AI344844, AI061334, AI679294, Z82205, AL049829, AC005666, Z93017, Z83840, AF111168, AC005696, AC006511, AC005971, AL049636, AC005488, AL031055, AL022721, AL035413, AC007774, AC005924, AC004797, AC005839, AL109628, AC002470, AL133246, AC005726, AC005841, AC007136, AP000354, AL109758, AP001053, AF064860, AL008635, AL035420, AC005037, AC005619, U80017, AL133448, AC004253, Z84487, AC005015, AL024509, AL096791, AC007878, AC004882, AL049832, Z83822, AP000555, Z97054, AC002094, AC002302, AL049766, Z82206, AC004862, AC002426, AL139054, AF207550, AL121769, Z85987, AC003982, AL079340, AC004678, AC005529, AC005829, Z93244, AP000116, AC004686, AL008725, AC003041, AC002476, L44140, AC005158, AL008718, AC006372, AL080243, Z84480, AC004590, AF134726, AC006285, AC002301, AC004019, AL078581, U47924, AR036572, U91328, AC004854, AC016025, AP000692, AC007388, AL049557, AC004878, AC002347, AC008372, AC004876, AC006327, AC005578, AP000501, AL033527, AC002073, AC006006, AP000547, AC000353, AC005089, AC006441, AC004765, AC004242, AC004150, AC005786, Z98884, AL121603, AC004983, AL024507, U85195, Z98950, AC002543, AF111167, AC005484, AC006274, AC007199, AL049872, AC004601, AC007688, AC003006, AC005070, AC002039, AF107885, AC004815, AL132987, AE000658, AB023049, AC003029, AL023804, AL022476, AC006088, AC005520, AC002115, Z83826, AL109801,</p>
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HSSMT70	629	530758	1 - 284	15 - 298	AA378674, and AA378675.
HSSMP20	630	854092	1 - 360	15 - 374	R70723, and AA378431.
HSSKD17	631	726525	1 - 552	15 - 566	W68188, AW248260, AW379441, H14177, R51748, N45444, AA009502, AA121499, AI750975, AA521345, AW204392, and AC005306.
HSSJQ60	632	975185	1 - 192	15 - 206	
HSSJP81	633	911334	1 - 541	15 - 555	Z43294, AA252498, AW371259, R07447, AA403066, F07754, and AL133017.
HSSJL22	634	871170	1 - 1260	15 - 1274	D31661, L41939, AF025304, L25890, L36643, and D37827.
HSSJK65	635	747891	1 - 742	15 - 756	AA010525, R94490, N59062, AI032097, R94491, and AI241480.
HSSJH78	636	773558	1 - 371	15 - 385	W58293, H17374, and AC004552.
HSSJA08	637	959336	1 - 559	15 - 573	AA516469, AI796388, and AA579963.
HSSGK12	638	970714	1 - 407	15 - 421	Z73988, and AL050347.
HSSGJ84	639	781975	1 - 492	15 - 506	H53756.
HSSGD96	640	796410	1 - 98	15 - 112	
HSSGD82	641	779899	1 - 558	15 - 572	R87893, and AL110228.
HSSGD56	642	608144	1 - 501	15 - 515	AA502843, AA470969, AI345157, AW150524, AL022323, AC002381, AL035555, AC005071, AL049776, AL022302, U91321, Z95152, AF165926, AC003029, AC006571, AC005154, AC005871, AC002402, AL096701, AC005899, U91323,

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HSSFU84	643	781973	1 - 623	15 - 637		HI3333, Z46049, and AC004590.
HSSFU84	644	888462	1 - 388	15 - 402		Z82214.
HSSFN08	645	959735	1 - 529	15 - 543		AA584893, M62144, AJ132917, AF158180, AF031075, AF031078, and AF030876.
HSSFK90	646	788687	1 - 534	15 - 548		AI633959.
HSSFB73	647	955200	1 - 322	15 - 336		R16937, and AC007537.
HSSEU40	648	891055	1 - 352	15 - 366		AA004732, and R45758.
HSSEP69	649	871211	1 - 356	15 - 370		AC005484.
HSSEI90	650	789157	1 - 373	15 - 387		H91190, AI903727, AW367564, AW376992, AW367618, AW367543, AW367594, and AL080172.
HSSEG25	651	679351	1 - 490	15 - 504		AA481165, AA034225, AW131736, AW137070, AA063633, AA844084, AA482038, and Z83845.
HSSER33	652	702701	1 - 530	15 - 544		H67629.
HSSEC79	653	775312	1 - 254	15 - 268		AA984057, AA084951, AB023138, M96377, and M96376.
HSSDQ07	654	880720	1 - 492	15 - 506		AI967980, AL035703, and U72207.
HSSDI03	655	924975	1 - 389	15 - 403		AA808840, W74796, W74722, AA723330, and AP000501.
HSSDH37	656	575460	1 - 256	15 - 270		AI869797, AA326034, AI689198, F01222, AA526683, AA032001, T30864, AA378474, AI590906, AA565319, AA856815, AA513851, AA364137, H93152, AA372106, N70449, AA343810, AI193417, AA225486, AA745302, AA714524, AA297698, AA384200, AA555232, AA086257, AI354333, AA831408, AA551067, AA745351, W44359, AI114557, R52008, AC005899, AC003029, AC007993, AC003025, AC004084, AF139813, AC000025, AC005527, AC006511, Z98750, AL035681, AC005529, Z94802, AC005399, AL135744, AL049776, AC007193, AC006277, AB001523, AC006388, AC000353, AL035659, AC006001, Z98946, AP000359, AC002351, AC004651, AL034417, AL109628, AL034420, AC002310, AC006023, AL035400, AC007731, AF038458, AC005365, AL049780, AC004491, AC005632, AC004973, AC005015, AL031056, AC005102, Z82206, AL133245, AC005841, AC005932, AP000689, AL121653, AP000279, AL031662, AC004019,



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HSSDC50	657	724696	1 - 244	15 - 258	HI6286, and R53150.
HSSCC14	658	600216	1 - 898	15 - 912	AI284640, AI281881, AI679782, AW276827, AA680243, AI334443, C75026, AI801591, AA720702, AA491814, AI368745, AW419262, AW162049, AI929531, AI683577, AI610159, AI732120, AI005388, AI471534, AW406447, AW088058, AW243960, AI469624, AI053672, AI471481, AA503015, AI962050, AI076616, AW303196, AW104748, AA649642, F36273, AA581903, AI339850, AW274349, AW022379, AW148792, AW166815, AW301350, AI358343, AI298710, AI434706, AI037683, AI567674, AL039958, AL048925, AI206785, AI138455, AI143242, AI564185, AI286356, AI625244, AL044858, AL119691, AI379719, AA613345, AA488746, AI355224, AI446638, AA394271, AA713815, AI927741, AI640702, AA178953, AA192740, AL042420, AW021583, AI246409, AW072587, AI133164, H71429, AI732186, AI696955, AI192631, AI355206, AI697208, AL044940, AW272758, AA521323, AL046898, AI674873, AW270270, AI110770, AI246796, AI376100, AI251002, AA665021, AI921649, AA620525, AW302013, AW270716,

<p>             AI890923, W79504, AA521399, AI061227, AI367975, AI364020, AA598586,              AA493708, AI049722, AI471543, AA587256, AA074130, AI471487, AA758934,              AI133636, N27584, AW089322, AI434311, AA084070, AI148277, M77974,              AI859251, AW073470, AW089789, AI134972, AI251436, AI568678, AW162489,              AA302963, AW406162, AI921188, AW440836, AC004743, AL031005, AP001172,              AC005037, AC006449, AC005324, AC004862, AC006241, AL031729, Z97053,              U62293, AC007450, AF042090, AB023052, AC005785, AL117352, AC004263,              AC005234, AC006468, AC002044, AC006115, AC006044, AP000513, AP000557,              AC003026, AL022322, AB023049, AC010206, U63721, AP000020, AP001054,              U91321, AC009516, AC005081, AC002542, AC005755, AC006487, AC009223,              AC005280, AP000553, AC005261, AL050341, AL078477, AC007676, Z83846,              AF134726, AD000684, AL031276, AL031965, AL021391, AC005218, AL096701,              AF088219, AC005520, Z99758, AP000556, AC006079, AP000302, AC008039,              AC005358, AC005341, AP000115, AC005412, AL096774, AL117258, AL034371,              AC002429, U78027, AF015147, AL031123, U67221, AC005011, Z86061,              AC006430, AL121603, AC004067, U07000, AC007308, AL031286, AP000503,              AL096768, AC006985, AC007263, U07562, AL035659, AC005844, AF077058,              AP000114, AP000046, AL035422, AC008079, AL008735, AC006213, Z94056,              AP000359, AC000026, AP000304, U66059, AP000047, Z98200, AL022476,              AC007842, AC005488, AC005288, AP000558, AL132987, AF123462, AC005778,              AF109907, AC002525, AC004491, Z99129, AL035420, AC005004, AP000351,              AL021707, Z98257, AC004492, AC005837, AL008629, AC002059, AL034561,              AL021368, AC004531, AL022311, AL049569, AC002365, AC005747, AC005231,              AL023575, AC006277, AL035417, AC007687, AL049759, AC004913, AL021393,              AC005900, AL031651, AC002452, AC004158, AL078472, U95743, X75335,              AC002549, AC005104, AL109753, AC004941, L48038, AC007731, AC004605,              AC006071, AC004675, AC005500, AP000555, AC006459, AL139054, U62317,              AC005043, AL035387, AC002460, AC003101, AC005664, AC002985, AP000348,              AL021940, AC007043, AF015167, AP000356, AC005971, AC005257, AC005531,              AC005175, AC004152, AP000950, AL109852, AC003074, AL031295, AP000689,              AC005699, AC005682, AF045555, AL035683, AL031848, U47924, AL049562,              AL021808, U80017, AC006211, AC004028, AC004253, Z95124, AC004987,              AP001053, AL021977, AC000075, AL049835, AC012599, Z82244, AL096791,              AC005072, AC022517, Z82210, AC004773, AF017104, AC007565, U18399,              AF037338, AL022147, AC006998, AC003041, AC005057, AC007151, AL031542,           </p>				
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HSSAZ04	659	933015	1 - 447		and AF001550.
HSSAY34	660	703345	1 - 399	15 - 461	AW104609, AA731470, AA378296, AA093496, AA648807, and AC005768.
HSSAP68	661	564334	1 - 1137	15 - 413	R35953, AA378260, AL137558, and AB033041.
				15 - 1151	AL041924, AA569648, AA595661, AW020150, AI801505, AA974503, AA577706, AI521525, AI310670, AL041375, AI479148, AI282253, AW162314, AL036896, AA669238, AW151541, AI251034, AA526542, AA287363, AI890297, AW338376, AA171400, AI250552, AA218684, AA515728, AA533025, N68677, AW302048, AL079734, AW020094, AW069227, AI224583, AW408413, AW021399, AW275432, AI251284, AI754653, AI926102, AA313025, AA084320, AI284543, AI537020, AI809776, AA583245, N26159, AA719564, AW410844, AI355246, AI879968, AW086291, AW162332, AA180056, AI625604, AA610826, AA218851, AA935827, AI904840, H77492, AI732151, AI223626, AA197089, AI049845, AA829036, AI791659, AA601674, AI345394, AI095197, AI003626, AI049643, AW439224, AA584765, AW419389, N95424, AI753131, AI310787, AI719298, AI254770, AI733523, AA659324, AA225406, AW274182, AI121039, AI349130, AI702049, AI453155, AA598443, AW022796, AI570236, AI915081, AI697235, AI654738, AI570067, AI216990, AC006312, AC007151, AC002477, AC005696, AF001549, AP000046, AP000114, AC006064, AL024498, AC005480, AC004263, AL022323, AC005911, AC005207, AL008718, AL020997, AC002425, AL031602, AL031053, AL136295, AL031311, AC006480, AL049869, AC006071, AC007057, AL049570, AC004526, AC007055, AF196779, AL031680, AC004659, AF001548, AC003101, AF207550, AC005231, AC002312, AC005736, AC006121, AL021918, AL034451, AC005049, AF109907, AL034379, AL021393, AL049780, AL050312, AC002310, AC005531, AC004000, AL133353, AL022336, AC005913, AC007688, AC003982, AL031229, AC002316, AL049694, AC005102, AL049757, AC005486, AC003043, AC003665, AC006487, AC005914, AL031685, AC016831, AL031662, AP000692, AC005702, AF053356, AC007371, Z94056, AC016025, AL133245, U95742, AP000359, AC002044, AL031295, AC007021, AC002400, AC007207, AC005081, AL080243, AC005015, AC008040, AC007376, AL078463, AC004671, AC005324, Z93023, AL022327, AC007685, AC005288, AC002369, AC007395, AL023803, AC006115, AC002470, AB023049, AP000503, AC010205, AL049759, AC004382, AC006449, AC005527, AL022476, AC005088, AC007637, Z86090, AL022396, AC007227, AL034420, AL035072, AL122021, AC004131, AC007686, AL031291, AL031284, L44140, AC006088, AC000025, U85195, AC006581, AC002375, AP000555, AC005755, AC004796, AC005225, AP000065, AL139054,

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HSSA189	662	875882	1 - 302	15 - 316	W92215, AA377828, A740584, N76763, T84274, R82785, T78575, R17095, T87269, R11236, and T79354.
HSSAE52	663	871244	1 - 167	15 - 181	AL472653, and AA377685.
HSSAA15	664	965347	1 - 796	15 - 810	AI110596, AA278446, R76143, AA312497, AA284193, AA355145, AA490794, AA377558, N79277, AA464226, AA363394, R24680, AA490748, AI902621, H56984, AA340607, R69950, AI830706, N78524, AW364076, H13787, AA366038, N80360, AA442589, AA046344, AA813247, AA215532, H45795, AW250076, AA147663, AI393282, AA282719, AI089657, AW043798, AI652874, AA557376, AW167542, AI982882, AA490235, AI143182, AI439663, AI017552, T89683, AW408401, AW402303, AA534702, AA284082, N51261, AI357897, AI089649, C14798, D60855, AA490509, AA864859, AA262577, AA812466, and AL133009.
HSRAY10	665	961237	1 - 731	15 - 745	AI565051.
HSRAS82	666	780222	1 - 259	15 - 273	AW385413, N78312, and U73168.
HSRAF70	667	524680	1 - 393	15 - 407	AB011100.
HSRAF11	668	967886	1 - 296	15 - 310	AC002133, and AC004587.
HSRAD72	669	539530	1 - 434	15 - 448	R06151, AA385070, AA398993, AA491011, H28273, R00914, H69631, H87597, R17024, AW362296, AA064980, AI065074, H28240, AA043619, AA032023,

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HSRAD65	670	871268	1 - 239	15 - 253		AL119835, AW163089, AW162617, AI928782, and AW162588.
HSRAD53	671	525490	1 - 321	15 - 335		
HSRAD49	672	722134	1 - 377	15 - 391		
HSRAD31	673	524845	1 - 235	15 - 249		AI394551, AA812658, and AA776285.
HSRAD10	674	968614	1 - 464	15 - 478		
HSRAD03	675	925505	1 - 303	15 - 317		AA312660, and AI474863.
HSRAB87	676	823174	1 - 325	15 - 339		AC002536.
						AA661583, AI536625, AA078084, AI803827, AI472453, AI932902, T60674, AA377621, AA302970, AA372389, F23307, AA496309, AA346485, AW192199, AA366936, AA459962, AA371410, AW194802, AC005944, AF000553, AC005895, AF165926, Z84718, AC005277, AC005358, AC005971, AL136295, AC005619, AP000351, AC005696, Z97054, AC004019, AC002470, AC005225, AC005280, AC006515, AC006511, AC007421, AC005940, U78027, AF129756, AC007731, AL049653, AL031255, AL035422, AP000505, AL133353, AC005071, AP000512, AP000114, AP000046, AC007546, AC020663, AC006946, AL133448, AL031280, AL049694, AP000555, AC005746, AC005821, AC005231, AC005500, AC005067, AL031722, AC006538, AC005911, AL022331, AL021154, AB023051, AC006509, AL035458, AL121934, AP000300, AP000045, AP001056, AL035405, U63721, AP000302, Z97056, AL049829, Z86090, AL121653, AF207550, AC004859, AL031733, AL008719, AC004814, AC002996, AL049757, AF029308, Z99716, AC005041, L78833, Z69917, AL080243, Z85986, AP000113, AL022324, AF196779, AC004841, AC007319, AC000025, AL008582, AC006057, AL031311, AC004983, AP000557, U91326, AL049872, AL132987, AC006449, AC004963, AC004883, AC005288, AC007066, AC005664, AL034548, AC002072, AL050318, AC005529, AC002504, AP000031, Z98946, AC003041, AP000345, AC004552, AC007298, AL031291, AL049759, AC005694, AL109627, Z92540, AC009516, U52112, AC004386, AC005095, AC006479, AC004448, AC005082, Z81369, AC005599, AC006992, AF205588, AC000041, AP000563, AC005755, AC005412, AC006539, AC006077, AL121603, AL049636, AL031432, AC003030, AC004134, AC004771, AL033527, AC002073, AL121915, AL139054, AC002401, AC007283, AC011311, AJ003147, AL132712, AL049539, AL133243, AL021977, AC007277, AC004099, AC002369, AC005519, AC000353, AC005606, AC003051, AL132992, AC005355, AC005695, AL035089, AL079295, U85195, AC005773, AC007308, AC004884, AC008041, AC002492, AC005527, AC008115, AC004217, AC007216, AC000379,

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HSRAB82	677	522945	1 - 388	15 - 402		AL031733.
HSRAB76	678	508105	1 - 393	15 - 407		AW003750, and AA608656.
HSRAB36	679	522946	1 - 376	15 - 390		AC005352.
HSRAB34	680	706996	1 - 399	15 - 413		L14561.
HSRAB08	681	960411	1 - 134	15 - 148		
HSRAA86	682	527194	1 - 415	15 - 429		Z66025.
HSRAA80	683	937640	1 - 446	15 - 460		AC006504, AC007788, AL020995, AL031393, and AC006118.
HSRAA64	684	955314	1 - 315	15 - 329		AC005924.
HSRAA51	685	522834	1 - 314	15 - 328		AA287418.
HSRAA39	686	719712	1 - 406	15 - 420		W57866, AA405363, AW068952, AI347952, AW338731, AW262930, AI650770, AI827045, AA406218, AI224572, AI983500, AI659859, AW139817, AI367100, AW029065, AA860374, N29563, AI683067, AI148585, AI963162, AA457121, AI830485, AW129125, AI983651, AI800368, AA115644, AI817037, H26177, AI590898, AI811420, AI963645, AA857298, H99276, AW088836, AI421113, H22014, AI753020, Z40200, F04312, AI751902, AA131162, AI698346, AI955784, AI290179, R22616, AI955793, AA834648, AA826157, AW057686, R62159, T33749, AW392341, H26176, AW274070, AI750657, R22615, AL096713, AB033033, AF182317, and AF182316.
HSRAA37	687	522837	1 - 444	15 - 458		AC007684.
HSRAA24	688	795855	1 - 465	15 - 479		T80334.
HSRAA23	689	524795	1 - 406	15 - 420		AI783911, AA502532, AA552724, AA481887, AA376358, AA604147, AA452887, F30310, H90878, R95840, AA584756, AA613754, N72170, AA559241, AL048275, AA192252, AA975894, AA181363, AI879951, AW265688, AI620585, AA194285, AI742168, AI358776, AA564925, AA936718, H62343, AA581247, AA339923, AA021429, AA018588, AA021428, AA722336, F00564, R73744, AI431513, AA019872, AA470567, AA708753, H78898, AA862253, AA747757, AA078830, AA605243, AI302156, AA481970, Z83844, AC006271, AC007226, AC006538, AC004841, AC005620, AC005531, AP000030, AC004131, AF196969, AC005696, AC006581, Z93930, AC005274, AL080243, U91323, AC000026, AP000694,

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HSLKB62	690	905738	1 - 1727	15 - 1741	
HSLKB37	691	929743	1 - 687	15 - 701	N68327, AW139202, AI350326, AI279786, AW339260, AA513265, H66480, H38171, AI187961, and H69151.
HSLKA06	692	934638	1 - 838	15 - 852	AI623826, AI202494, and AI137429.
HSLJJ62	693	742895	1 - 423	15 - 437	R10605, T97572, and R91642.

HSLJF33	694	938811	1 - 542	15 - 556	T12297, and T12296.
HSLJD02	695	965826	1 - 942	15 - 956	AW360811, AW366296, AW375405, AW177440, AI905856, AW178893, AW377671, T03269, AW177501, AW177511, AW360844, AW360817, AW352117, C14389, AW179328, AW375406, AW378534, AW179332, D58283, AW377672, AW179023, AW178905, D59859, AW352170, D80022, C14331, D80166, D80195, D80193, D59927, D59467, D51423, D59619, D80210, D51799, D80391, D80164, D59275, D80240, D80253, D80043, D59787, D80227, D59502, AW378532, AW367967, D81030, D81026, AW178980, C14014, D80212, D80196, D80188, D80219, AW178775, AA305578, D80038, C15076, D80269, D59610, AW377676, AA305409, AW352171, D57483, C14429, D51022, D50979, D50995, AW177731, D80366, D59889, AW178907, AW178906, AW178762, D80248, D80045, D80132, AW179019, AW179024, D80522, D80024, D80134, AA514186, AA514188, D80378, D51060, D80133, D51097, AW177505, AW179020, AW178909, AW177456, D80251, AW179329, AW177733, AW378528, AW178908, AW178754, AW179018, AW352158, D58253, AW352174, D80268, AW179004, D80302, AW178914, AI535850, C75259, D80439, D80247, AW178774, T48593, D51103, D88547, X82626, A84916, A67220, D89785, A62300, A62298, Y17188, AB028859, A78862, D34614, D26022, AJ132110, AR018138, AR008278, X67155, Y12724, AF058696, A25909, A94995, AB012117, AR025207, I18367, AR008443, I19525, AR066490, A85396, D88507, AR066482, A44171, A85477, A86792, AR066488, X93549, A82595, AR016514, D50010, D13509, AR060138, A45456, A26615, AR052274, Y09669, AR060385, AB002449, AR066487, A43192, A43190, AR038669, AR008408, and AR060133.
HSLIJ48	696	721248	1 - 916	15 - 930	AL119990, AA524531, AI459232, AW295852, AW274849, AI990971, AI086621, AI703399, AI582316, AI887899, AW444954, AI198620, AI201159, AA769116, AA908833, AI769819, AI761662, AI678189, AI638810, AW001104, AW339272, AI025272, AW151222, AW015232, N30310, AI797112, AA781447, AW083242, AA291544, AW003604, AA831760, AI027612, AI624665, A W276610, AW168171, AW170708, T62956, AA442455, AI807572, AW080508, AI052790, AW378235, AA827853, AA737447, AI969056, AA465529, H03505, R78862, AW205495, AA515398, T88738, AI972735, AA436647, AA805386, H03615, N56642, AI825714, AA293351, AW292091, AI473377, AA404571, AI349471, T63206, R79349, AA399447, Z38283, AI582475, AA252529, AA252574, AA708728, AI670981, AA429843, C06324, AA748807, AI650622, AW392315, and D20600.
HSLIG07	697	952493	1 - 766	15 - 780	N31935, AI433732, N20982, AA736780, AA721230, AA460997, and AA018340.



HSLJE03	698	923393	1 - 636	15 - 650	AA164206, and Z98049.
HSLJC21	699	670359	1 - 499	15 - 513	H22544, AI204929, and H46842.
HSLHZ82	700	779067	1 - 512	15 - 526	H72516.
HSLHZ10	701	963808	1 - 294	15 - 308	T57527.
HSLHV27	702	964075	1 - 999	15 - 1013	T03269, D80212, D58283, D80166, D80195, D80193, D59927, D51423, D59619, D80210, D51799, D80391, D80240, D80253, D80043, D80227, D59859, D80196, D80188, D80219, D80269, D80038, C14429, D59889, D81030, D80366, D59502, D57483, D80022, D59275, D80045, D59610, D80024, AW178893, D80378, D50979, D50995, AW177440, C14389, AW179328, D59787, D80241, C14014, C75259, D80164, D51060, AI905856, C14331, D80134, D59467, AW378532, C15076, D51097, AW178775, AW177501, AW177511, AA305409, AW352158, D81026, AA285331, F13647, AW178762, AW352117, D80949, D80168, AW360811, AW176467, D51022, D58253, D80522, AW377671, AW377672, AA305578, AW375405, AW360834, AW360844, AW366296, AW360817, AW179023, AW375406, AW178905, AW378534, D80248, AW179332, AW352172, AW177731, D59695, D80251, AW352171, AW377676, AW179019, AW352170, AW179024, AA514188, AW178907, AW179220, AW177733, AW177505, AW179020, AW178909, AW177456, AW378528, AW179018, D80268, AW179329, AW178908, AW178754, AA514186, D80133, AW178906, AW178980, AW367967, AW179004, AW178911, AW178914, C05695, AW352174, AW178774, D80132, D80302, AW178983, T48593, D80439, D80247, AW177723, AW378533, D80157, D51103, AW367950, AA033512, AW178986, D45260, C06015, AI535850, C14975, AW378542, D80314, C03092, AW360855, AI525923, AI525913, AI525917, AA514184, AI535959, A84916, A67220, D89785, A62300, A62298, A78862, AI132110, X67155, A25909, Y17188, D26022, D34614, AR025207, D88547, X82626, AR018138, AB012117, Y12724, A85396, AR066482, X68127, A44171, AF058696, A85477, I19525, A86792, AR008278, X93549, AB028859, U87250, A94995, AF135125, AR008443, I50126, I50132, I50128, I50133, AR016514, A82595, AR066488, AR060138, A45456, A26615, AR052274, D88507, AR064240, A43192, A43190, AR038669, A30438, D50010, Y09669, AR060385, I18367, AR066490, AB002449, AR066487, AR008408, AB033111, Y17187, A63261, D13509, AR060133, AR062872, A70867, U87247, A64136, A68321, Z32749, AR016691, AR016690, U46128, U79457, AF123263, I14842, X93535, and AR008382.
HSLHG49	703	722570	1 - 455	15 - 469	T76925, and F13028.

HSLHC40	704	710681	1 - 386	15 - 400	H87626, and H87632.
HSLGY08	705	959371	1 - 459	15 - 473	H52847, and U73638.
HSLGQ48	706	720956	1 - 450	15 - 464	R14758.
HSLGP07	707	953305	1 - 430	15 - 444	H52460.
HSLGO19	708	668634	1 - 530	15 - 544	T69707, AI364440, N48142, and AI193460.
HSLGN78	709	773565	1 - 345	15 - 359	AA648821, AI937873, AW241962, AA085600, AA743475, and AA618255.
HSLGN52	710	466026	1 - 268	15 - 282	N44280, and AF030339.
HSLGK46	711	719031	1 - 479	15 - 493	AI929533, AA143673, AF160973, AB032994, AL136549, and AF162472.
HSLGK26	712	929286	1 - 594	15 - 608	R02405, AI902990, AL049742, and AB033071.
HSLGK23	713	675266	1 - 447	15 - 461	AA761431, W23694, and W35274.
HSLGI37	714	708824	1 - 438	15 - 452	R14817.
HSLGI76	715	770035	1 - 643	15 - 657	W03269.
HSLGI67	716	465989	1 - 681	15 - 695	R15431, R43754, R41977, AI684818, AW263190, R20728, and AA764976.
HSLGH70	717	871888	1 - 613	15 - 627	AA020737, AL120362, T04912, AI207884, and AL120567.
HSLGG86	718	784703	1 - 573	15 - 587	R13205, F06363, Z42917, Z42916, and AC005550.
HSLGG79	719	775146	1 - 469	15 - 483	N49335, N32155, AI378923, AA825350, AI168537, T75454, AA553340, and AC003086.
HSLGA79	720	774051	1 - 487	15 - 501	T89229.
HSLGA45	721	717776	1 - 198	15 - 212	AA456710.
HSLGA24	722	955333	1 - 793	15 - 807	
HSLFU18	723	666405	1 - 975	15 - 989	AI948585, AI091275, AI768335, AA002188, AA054389, AI422809, AA625455, AA152352, AA504767, AI091665, AI274082, AI151107, AI356672, AI276227, AW363928, AW293599, AI379300, AA028994, T06356, AI401834, D25946, Z41039, AA152353, H09081, AI695174, AL118909, AA429474, AI079113, and AC008154.
HSLFT29	724	680451	1 - 448	15 - 462	
HSLFN96	725	796375	1 - 267	15 - 281	
HSLFI01	726	876881	1 - 458	15 - 472	R74609, AW080754, AL049611, and D31762.
HSLFD70	727	757319	1 - 501	15 - 515	AA463820, AW177073, AA235749, and AI940206.
HSLFB84	728	783130	1 - 422	15 - 436	H02965.
HSLDW24	729	779689	1 - 442	15 - 456	AW237453, N56967, N47347, AA436760, R96401, H73070, and AC005082.
HSLDT25	730	949079	1 - 1531	15 - 1545	
HSLDR18	731	578926	1 - 371	15 - 385	
HSLDR05	732	932128	1 - 220	15 - 234	

HSLDP66	733	866331	1 - 389	15 - 403	AW151855, AC006597, AC004796, AC005844, AC005740, AC007563, AL049780, AC005015, AC006530, Z99716, AP000350, AC002365, AC004408, AC005747, AC004552, AC005663, AC007057, Z83820, AC005670, AC005242, AC009501, AL034343, and AC004125.
HSLDO01	734	916969	1 - 303	15 - 317	
HSLDM82	735	780055	1 - 533	15 - 547	T53015, T53016, and U88969.
HSLDF25	736	430328	1 - 541	15 - 555	
HSLCY75	737	766533	1 - 536	15 - 550	W88780, and AC000078.
HSLCX61	738	742031	1 - 538	15 - 552	H19015, R24546, and AC007676.
HSLCF96	739	637670	1 - 1575	15 - 1589	
HSLBW39	740	705630	1 - 419	15 - 433	AA190333, and AB029001.
HSKZE91	741	790166	1 - 531	15 - 545	AI904945, T48340, AI921328, AI147425, AW264955, AL079935, AF111163, AC004765, AL109827, AP000503, AF134726, AJ003147, AP000201, AF124731, AP000097, AL031295, AC000105, AC002565, AC006367, and AC004032.
HSKYG48	742	721631	1 - 294	15 - 308	AI204981, W23546, AA862243, AA579469, AA749235, AA572960, AA780929, AA808263, AA814778, AI446474, AA508873, AA857381, AL043289, H10143, AW022317, H29019, AW082744, AA634786, AA655005, T92957, AA577748, AW068394, AA384039, AI870204, AI623899, AA122028, AL120708, AA502175, AA426277, AL120897, AI216054, F17700, AI916335, F23327, AI754064, AI446464, AA558298, AI355119, AI908093, H45320, AA467988, AA492313, H10859, AA364814, AL133553, AL031289, AC007298, AC009479, Z98755, AC004815, AC005046, AP000348, AC008249, AL133244, AL133163, AL024498, AC008044, AL035455, U91323, AC002347, AC006965, Z97053, AL022318, AC005520, AC002477, AL031431, Z95889, AC007564, AC005089, AP000552, AF109907, AC002395, U95742, AC003029, AL035685, AL020993, AC005696, AB023049, AC005856, AC005837, AL031432, AF117829, AL109984, AC005071, AL117352, AL096864, U95740, AC004972, AC004675, AC009510, AC007536, AC005664, AL031012, AL050318, Z84466, AL050307, Z98051, AF190465, AL022312, AP000355, AC005632, AC005781, AC004149, AL132712, AF088219, Z85986, AF207550, AC000085, AC007216, AC005339, AP000117, AC005358, AL121653, AC007664, AC005291, AL035072, AC005412, AL021917, AC005776, AC000003, AC006450, AL031433, AF152365, AL031447, AF196969, AC004150, AC004797, AC002301, AL049694, AC005228, AC012384, AC006547, AC003071, AL031257, AP000553, AL049836, AC009516, Z98949, AC005057, AC003102, AC006285, AL031848, AC005907, AC004024, AC005538, AP000512, AC003992, AC010382,

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HSKXA69	743	754258	1 - 470	15 - 484	T71620, AA534420, AA831032, AA594106, AI263883, AI761286, AA983957, AI001173, T92198, AW004790, and T89254.
HSKKE11	744	965857	1 - 231	15 - 245	W16981, AF195534, and AF005355.
HSKJR15	745	866396	1 - 394	15 - 408	AI287342, N49215, and AB020629.
HSKJC88	746	866402	1 - 543	15 - 557	AI420428.
HSKII90	747	788894	1 - 628	15 - 642	AA216387, AA228676, T63548, and T63473.
HSKHZ47	748	720286	1 - 623	15 - 637	AA001179, AA001429, AA018483, AL1119995, and AC007228.
HSKHT93	749	957866	1 - 437	15 - 451	AA252410, AA095264, AA310368, AA282860, R88254, AA131559, AA043465, AA319576, AA315504, AF091871, and AF117815.
HSKHP10	750	964568	1 - 316	15 - 330	AI810136, AA974689, AA889167, and AL137442.
HSKGS69	751	755046	1 - 321	15 - 335	AI094227, R02713, T86217, W92159, W86709, AA885954, and W86575.
HSKEH21	752	941976	1 - 952	15 - 966	AI675047, and U59429.
HSKDC06	753	935452	1 - 318	15 - 332	R82607, R64237, and T92293.
HSKCR54	754	922730	1 - 743	15 - 757	AA203533, AW129778, W67725, AI760143, AI760154, AI076011, AI141700,

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HSKCD43	755	714389	1 - 492	15 - 506	AA424097, AA452654, R02449, AF033120, AF033121, and AF033122.
HSKBW86	756	785783	1 - 351	15 - 365	
HSKBW62	757	521937	1 - 316	15 - 330	AA653323, AA598964, AA653202, AI732164, AI821721, AA745570, AA610482, AA569206, AA364953, AI624800, AI092525, AA564510, N25034, AC004253, Z83843, AC004386, Z95125, AI137312, AC005899, AI049709, AC007690, AC005746, AC003102, AC005616, AI133353, AC002456, AP000507, AI021154, Z97206, AC004699, AC004905, AC005844, AC004970, AC002326, AC004887, AC003047, AC005031, AC004999, U80017, S83170, AI031662, AC007314, AI035420, AI034561, AI135744, AC005011, AI022165, AI035090, AC006312, AB000880, AC006441, AC005903, AI031905, AI079342, AI139054, AC007151, AI078581, AC004491, AC004601, AI035587, AI050348, AI080243, AC005684, AC004832, AC004851, AC004938, AC009516, AC005200, AC006111, AC002978, AC002123, AC007425, AI078460, U82828, AC018633, AC004217, AC002465, AC002300, X76498, Z97055, AC007999, AC002302, AI035691, AI031003, AC007207, AB001523, AC002418, AC003010, AC008372, AI035361, AF111169, AC005553, and AI021578.
HSKBW21	758	671383	1 - 128	15 - 142	AI218427.
HSKBV67	759	561585	1 - 245	15 - 259	
HSKAE10	760	968508	1 - 680	15 - 694	AI478821, AI034114, AW057617, and AI034113.
HSKAC29	761	535402	1 - 362	15 - 376	AA381761.
HSICA03	762	925252	1 - 450	15 - 464	AA813174.
HSIAY64	763	866540	1 - 301	15 - 315	T59788, and T59655.
HSIAB49	764	723261	1 - 325	15 - 339	H60179.

HSHCL04	765	840406	1 - 1575	15 - 1589	AL282710, AA469327, AW272815, AC007637, AL021154, AC007055, AL049780, AC007216, AL109827, AL035072, AC002369, AL096791, AL021453, AC002425, AP000501, AF196779, Z82206, AL031311, AC005837, AC006241, AC005409, L44140, AC004531, Z84469, AL133448, AC005520, AL022316, AP000689, AC005740, Z98941, AC005562, AC005914, AC004686, AC007263, AC004905, U91318, AC011311, AC005736, AC004525, AL110502, AC004217, AC004895, AC005899, AC005288, AC007298, AC005553, AL121658, AC005920, Z99716, AF109907, AC006064, AC005972, AL031447, AC005696, Z98742, AL133485, AC007225, AC004782, AC002492, AC004125, AL035420, AL022329, AC004985, AL008582, AC005280, AC004841, AC005911, AC018633, AC006006, AP000046, AP000140, and AL022320.
HSHCK86	766	785392	1 - 564	15 - 578	
HSHCJ63	767	468536	1 - 489	15 - 503	
HSHBU07	768	866636	1 - 443	15 - 457	
HSHAH05	769	932689	1 - 379	15 - 393	H02663.
HSCAF60	770	537444	1 - 372	15 - 386	AL684502, and AL080250.
HRDFU03	771	924698	1 - 352	15 - 366	R07659.
HRDFH46	772	590391	1 - 523	15 - 537	AA102589, AA804174, and AA026519.
HRDFG13	773	925350	1 - 237	15 - 251	AA443411, Z99716, and AJ236681.
HRDFF47	774	740594	1 - 101	15 - 115	H81628, N66263, and AL049835.
HRDFD56	775	733556	1 - 447	15 - 461	AW051571, AA662497, AI022097, AA779814, AA649495, AA621426, D62952, AA621628, AI470588, D79237, N50823, R51630, AA019034, R42166, and AA887956.
HRDFA03	776	867122	1 - 974	15 - 988	AI054414, AI608771, AI204309, AL037632, AA290878, AI791227, AA577824, AA714224, AI871954, AA547979, AI445582, AW405593, AA287259, AL048969, AI133516, AA206629, AI922805, AA601425, AI907046, AA838140, AW238345, U51704, AI061646, AL042310, AA443390, AA708108, AA429020, AI581006, AI281401, AI925321, AA737309, AW247819, AA829044, AA311156, AA524604, W96277, AA610433, AL135377, N49425, AA595093, AI110760, AA581471, AI679782, AA603315, AL079869, AA224525, AL138265, AA209415, AI354847, AI889426, AA287618, AA429197, AI745133, AC004797, AC005015, AP000134, AP000212, AL031281, AC009516, AC006211, U95742, AC007227, AC006285, AF047825, AP000692, AP000030, AL049569, AF109907, AC004019, AL049776, AL024507, AC007193, AL022238, Y10196, AC007216, AC007637, AC005519,

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HRDEZ73	777	774414	1 - 371	15 - 385	<p>H26725, H22204, R48422, H40444, AW299397, AI125783, AI003778, AA470331, AA470347, AA468450, AA468277, AA468204, and AI924555.</p>

HRDEX24	778	867123	1 - 750	15 - 764	AI347412, AA098880, AA099225, AI473261, AI308141, and AI468639.
HRDER90	779	789140	1 - 414	15 - 428	AA084891, H82037, T85036, R94550, and R01653.
HRDER35	780	707569	1 - 447	15 - 461	W02017, AB011399, AL049698, and AB016897.
HRDEP20	781	690456	1 - 878	15 - 892	N41324, AA196645, W80987, N56686, AA317626, H71355, AA305440, AA150080, AI885648, W92648, AA070703, AA824341, AW410573, AW157530, AL040266, AA045127, AA043642, AA368590, AA325559, AA587915, AW250790, AA778651, AA317723, AW410572, AI139138, AW007464, AI819989, AW188549, AI951992, AI951978, AA036715, AI677931, H92998, AI364379, AI758826, AA303613, AA749431, AW162769, AA584288, AI376410, AI373112, AA383234, AA977318, AI187131, AI768324, AI076148, AI934676, AA150015, AA057355, W70033, AA682387, AA196549, AI000432, AI040155, AA513466, AA946608, AI038499, AI279549, AA778720, AI887548, R60037, N86794, W94564, AA487107, AI758476, AW273537, AI077415, AA836837, AW103741, AI199096, AI439996, AI278114, AI038357, H94227, AA186980, AI253749, AI700221, AW004637, AA045098, AI200368, and T35014.
HRDEK53	782	867137	1 - 275	15 - 289	AA703174, AC005585, and AC004832.
HRDEI33	783	487523	1 - 110	15 - 124	AL034344.
HRDDX67	784	460145	1 - 438	15 - 452	AC007541.
HRDDX01	785	921501	1 - 376	15 - 390	AI871189, AA512915, AI636339, and AI017463.
HRDDU41	786	712572	1 - 297	15 - 311	AI280574, AA329535, AI559583, AW089016, AI983047, AA743968, AI453160, AI554725, AI564294, AI436330, AA715891, AA657910, AA613775, AA837715, AA287502, AA632765, AI471467, AA573693, AA326904, AI306717, AA643451, AA636102, AI628859, AI049701, AA577824, AI762528, AI253376, AW007424, AA809153, AA017240, D51809, F00688, AA552989, AW073498, AI929410, AI753672, AI049512, AI925978, AI750950, AL043212, AA993165, AI280535, AA857812, AA233951, AI590598, AA598734, AA099840, AL041019, AW265279, AW084100, AI244356, AW188791, AA608520, AA704393, AL041018, AI569363, AI002762, N22153, AI524471, AA558404, AA643441, M86139, AI417586, AI225179, AL138199, AI564301, T74524, F31654, AA679353, T40629, AA846923, AA084506, AI609972, AA302978, AI255004, AI049630, AI255015, AI569546, T74259, H74326, T92803, H38769, AI537800, AW263867, AA223910, AA230146, T90477, AL120543, AI061313, AW084173, AC004605, AC007283, AP000501, AL031659, AC005227, AC005180, AC006515, AP000365, AL049779, AC010206, AF003626, AC004707, Z95152, AC007193, AC004662, AL035555, AL031275, AL031407, AC004694, AJ003081, U80017, AC004531, Z99943, AL022238,



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HRDDR39	787	867151	1 - 210	15 - 224	AA422067, AI822098, AI341461, and AI338541.
HRDDQ55	788	490884	1 - 598	15 - 612	AW410844, AW148821, AL121039, AI702049, AI890283, AW265468, AW162314, AA640305, AI567676, AA765899, AA507623, AW162332, AI064968, AI884404, AW275432, AI174703, AA601336, AW021674, AA280886, AA515727, AW151541, AI252005, AI254463, AW439224, AA831426, AA728954, AA313025, AI570067, AI250333, AI538404, AA524604, AW192930, AI090377, AA935827, AA558488,

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HRDCD44	789	715769	1 - 558	15 - 572	W03563.
HRDBH52	790	728715	1 - 559	15 - 573	W69216, R85388, AA677237, and AW295702.
HRDAB42	791	800333	1 - 415	15 - 429	AA372217, and N74721.
HOSOW01	792	914804	1 - 472	15 - 486	R12246, T97409, H20317, F10552, AA642698, AA463715, T03808, AA135561, AI912860, T16035, H17063, AL109623, AC010206, AC004787, AL031186, and AC007358.
HOSNO25	793	974291	1 - 601	15 - 615	AC005243.
HOSMP95	794	948496	1 - 591	15 - 605	R09369, N78208, N59653, AW295483, T85232, R09252, T89192, AI638845, AI824892, AF161355, AC004500, and AF197927.
HOSGN29	795	830653	1 - 420	15 - 434	AA463363, AA490561, AA452944, T66840, AI907242, AA774254, AA972623, AA459531, AA355833, N77376, Z20330, AA088535, AI561196, H90342, AA610050, AA883211, H90382, and AF155107.
HOSFV77	796	856933	1 - 645	15 - 659	AI302244, AI376858, AA744868, AI655166, AA206365, AI016092, AW117621, AL135188, AI473834, AA442880, AI218992, AW440891, AI619652, AI218976, N58875, AA005386, AA515059, R83118, T66299, R37419, AA227169, R66694, N54853, R67572, AW168764, AI862971, R83130, AA782861, R27978, T95799, AA731049, Z38308, AA813893, AA256649, R28234, R66224, and AL035411.
HOSFU59	797	739262	1 - 424	15 - 438	AA076237.
HOSFL57	798	734709	1 - 351	15 - 365	R21661.
HOSFL07	799	953183	1 - 677	15 - 691	H80558, AA011699, AA249550, N50173, AA720594, AA812006, N53417, AI985322, and AB032996.
HOSFK40	800	711140	1 - 566	15 - 580	AA056618, AW015136, AI640750, AI814601, AI215460, AI478294, and T98138.
HOSFI46	801	719021	1 - 297	15 - 311	N55220, AA488250, W92994, AA897297, D81949, AP000495, and AC002076.
HOSFC66	802	750560	1 - 671	15 - 685	W52745, AB023145, and AB028449.
HOSFB04	803	615200	1 - 412	15 - 426	R15372, H16359, and R19326.
HOSDR12	804	971169	1 - 447	15 - 461	Z99943, AC004000, L78810, AL117352, AC006387, AF155238, AP000556,

						AP000557, AC003006, AL031685, AL049759, AC004590, AC007371, AC004069, and AR038753.
HOSDQ78	805	858983	1 - 488	15 - 502		AC006474.
HOSDP27	806	682113	1 - 500	15 - 514		N26610.
HOSDG79	807	781787	1 - 913	15 - 927		W95020, R91323, H70373, and AI655142.
HOSDA04	808	951842	1 - 525	15 - 539		AA846729, AI028108, AA846827, AI609525, AA724378, AA843409, AW195335, AI949374, AI129292, AA706724, AI806599, AA700507, AI031774, AI478383, AW003724, AA056023, AA029907, AI206246, AW197629, AI082553, AI026964, AI023934, AI026963, AW235807, AI079146, AI056148, AA424153, AA854249, AA843263, AI022608, AA479110, AI802270, N90579, AA846140, AI168397, AI031992, W39235, AA846163, AI022871, AI335584, N52355, AA723602, N35347, W04599, W15275, AI026070, AA044387, AA452000, AA772698, AA724104, W45008, N52362, N94993, AI478133, R54828, AA772128, W32433, AA479261, AA411010, D79933, D79420, AI382712, AA056071, C00297, N75133, D62903, and AL110152.
HOSCV06	809	960555	1 - 346	15 - 360		AI610013, AI090186, AW173233, AI127920, AA058965, AA099683, AW082370, AA146976, AI873263, T94367, AA099684, AA136188, AA137215, AA279168, and AL133104.
HOSCT25	810	783692	1 - 449	15 - 463		T83223, AI074110, W47135, N27470, W24127, AA284235, Z19637, AA936569, and A74325.
HOSCP67	811	753874	1 - 505	15 - 519		AA181657, and AA190577.
HOSCO73	812	764756	1 - 305	15 - 319		T90400, and AC008063.
HOSBY89	813	787182	1 - 429	15 - 443		W03298, AW453073, R91771, AA248939, and AA281702.
HOSBX46	814	719414	1 - 352	15 - 366		AI435472, N52787, N48806, AL049781, AB002309, and U17195.
HOSBX34	815	706769	1 - 533	15 - 547		HI0526, R20107, F05110, and AC008009.
HOSBR53	816	728525	1 - 613	15 - 627		H29345.
HOSBO34	817	706770	1 - 474	15 - 488		AA167280, AI269650, and AW404853.
HOSBM55	818	732550	1 - 528	15 - 542		N70015, N70098, W00901, R17917, W00930, R18009, AB014087, AC004188, and AP000516.
HOSAY52	819	728759	1 - 352	15 - 366		AA249054, AL118892, N45598, AA628647, AI016287, N57609, AL049781, AB002309, and U17195.
HOSAX03	820	960942	1 - 931	15 - 945		AA400703, AI684638, AW070184, AI090864, AW183803, AA400657, and AW293645.
HOSAL10	821	968710	1 - 299	15 - 313		AA075375.

HOSAI41	822	712708	1 - 1063	15 - 1077	AA203712, AI807483, AA203713, AI088364, AI131250, AA489726, AA489625, AA004409, AA705699, AA723797, AW293365, H95647, T98715, H82415, and AI022074.
HOSAH30	823	693406	1 - 479	15 - 493	HI9428.
HOSAF19	824	672078	1 - 516	15 - 530	AA147082, and AA312956.
HOHEN28	825	686034	1 - 444	15 - 458	N33237, AI631133, AI917082, AI657012, AI624839, AA902453, AI655635, AI273682, AA729233, H27969, AA761232, N21684, AA417084, T06849, AW004990, AI280456, AI865276, AI638369, and D31765.
HOHEG71	826	760051	1 - 529	15 - 543	AA233884, and AA232830.
HOHDF94	827	793970	1 - 702	15 - 716	AA081832, and AB018257.
HOHCV57	828	734413	1 - 488	15 - 502	N76235, AB007936, and AL109755.
HOHCL29	829	634778	1 - 381	15 - 395	AI525843, AI541231, AI541114, AI541109, AI547179, H41687, AA984744, AI547043, AL044967, AI547164, AA094680, AA525444, AW014590, H18262, H50911, H45071, H41335, H42388, F33456, AI979115, AI547122, AA484568, AA285311, AA090063, AI498779, AA096319, AA426205, M27358, K01364, X00686, X56974, X82564, M10098, K03432, U13369, X03205, AF000381, K01593, M29839, X01117, V01270, M11188, X06778, J01876, X00640, X59733, X59734, K01373, X04025, AF115860, M97576, J00999, X02995, AJ279506, M91183, M15821, L11288, M91181, AJ270030, X98837, AB029314, X98838, X98841, X98839, X98843, X98842, X98846, M91180, X98840, X98844, M91182, AF169014, AB016657, X98836, AF030250, M97575, M97573, M59398, U76257, U11437, M59400, M91179, Z61867, M59402, M59401, AF021880, M59384, M59387, M59392, M59390, M59383, M59403, M59393, M59397, X98845, M36006, M59389, M59385, AB016658, M59386, M16759, S60585, AB016659, M59395, M59391, D38360, D38357, D38341, D38358, D38354, D38363, D38362, M59396, M59388, D38359, M59399, and M59394.
HOHCH52	830	588375	1 - 555	15 - 569	R63803.
HOHCG79	831	859029	1 - 453	15 - 467	AI025117.
HOHCD58	832	973105	1 - 442	15 - 456	
HOHBZ27	833	588364	1 - 453	15 - 467	T26461, R12434, and AI0909064.
HOHBY26	834	588358	1 - 464	15 - 478	AA190664.
HOHBV67	835	718562	1 - 527	15 - 541	AA464946, AA045533, AA058869, Z43315, F07427, R34556, D20922, and R17869.
HOHBS10	836	964324	1 - 396	15 - 410	AW072006, AA992322, AW183466, AI590479, AI610065, AA524829, H53828, AA828610, AA476397, AA572713, AA431949, AW440299, R49657, AI436608,

HOHBP36	837	708158	1 - 468	15 - 482	<p>AI114557, AA480574, AA847702, AA482953, Z84469, AC005899, AC005822, AC006079, AC008125, Z93016, AC002544, AC004408, AC005411, AJ011930, AC005996, AC007773, Z98257, AC002553, AC006211, AL035086, AC006088, AC005332, AC004263, AC009225, AC004841, D87675, AL133243, AC004884, AC004460, AC020663, K03176, K03178, Z99716, AP000961, AC005747, AC006080, AC004659, AC006978, Z84480, AC002316, U96629, AC006959, AC005186, AC006318, AC007050, AF165176, AL022326, Z68164, AF008191, AF017104, AC004230, AJ003147, AC002091, AC011504, and AL022329.</p> <p>N53160, H56717, N58596, H56640, W27084, AA516214, F19606, AA515728, AA558487, AA278482, AI823533, AI823535, AW057873, AW151288, AI356264, Z54073, AF001548, AF205588, AC004263, AC004982, AC006948, AC005081, AC005476, AC002390, AL049843, AL009181, Z82215, AC007312, AL049757, AF129756, AC003010, AC009225, AC006312, AP000555, AC004601, AL021878, AC005684, AL035411, Z98949, Z93020, AL049709, AF134726, AC004985, Z84476, AC003101, AC004820, AL109627, Z85987, Z93241, AC009405, AL049613, AC005036, AL109753, AP000091, Z95115, AF196779, and AL008721.</p> <p>AA489227, AA490533, AA504306, and AA490534.</p>
HOHBN56	838	859041	1 - 897	15 - 911	
HOHBL35	839	973238	1 - 462	15 - 476	
HOHB184	840	782908	1 - 363	15 - 377	<p>H46912, AA287471, AA399188, AW007707, AL036600, AA025639, and AA405089.</p>
HOHBB90	841	588308	1 - 448	15 - 462	R76965, AI077565, AA452929, AI393755, and AL035455.
HOHAV60	842	489007	1 - 827	15 - 841	N20939, AI337242, H68935, AI224489, F27732, F37358, and AC007279.
HOHAT59	843	867949	1 - 454	15 - 468	AI124699.
HOHAT11	844	966727	1 - 622	15 - 636	U83208.
HOHAQ65	845	859057	1 - 501	15 - 515	<p>R06584, R06638, AA086435, AW408596, AA111870, C14480, AA279649, AI680547, AA608570, AL135363, AA595661, AA158018, AA554257, AA205436, AW162227, AA470512, AA599423, AA315361, AA722336, AW082098, AA470559, AA569053, H64278, F33037, AA348399, AI298079, AA378489, AI271762, R81167, R89129, AW069537, AI440037, AA368659, AC005042, AC005207, AC002425, Y08864, AC005531, Z49236, AP000099, AC005598, AL109865, S42653, AC007182, AL034420, AC007637, AL022720, AP000036, AC007738, AP000553, AC004820, AC004531, AC008273, AF069074, U91326, U68041, AC003684, AL049712, AL021453, AC007563, AC005746, AC008015, AL031228, Z49862, AL031681, AF181897, Y10196, AC007050, AL023494, AL031311, AL049776, AC004900, AL031291, AC002492, AL096791, AP000133, AP000211, AC006211, AC002477,</p>

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HOHAM6 6	846	859058	1 - 545	15 - 559	H02088, R30796, AI904000, and AW175694.
HOHA111	847	947140	1 - 4073	15 - 4087	AA424371, AA417690, N72255, AA417582, W02998, AI378916, AA424511, and AF086109.
HOHAE76	848	494001	1 - 453	15 - 467	T59559, and T59513.
HOEOA28	849	859156	1 - 786	15 - 800	AI276895, AW026397, AA053296, AA054752, AA789119, AI745474, AA744964, AW087227, AW379213, and AC002519.
HOENH06	850	934095	1 - 844	15 - 858	AW007160, AA393649, AI022457, AI139147, AW386744, R40518, HI4594, Z40081, F01575, R48161, F10287, N93352, AA468505, AA614254, AA228368, AA468371, AA230025, AA467760, AA224889, AA228269, AA298789, AA838161, AA599710, T47138, AI355385, AA381754, AI418967, AA224815, AI270370, AA197218, H63066, AW057873, AA259267, AA558404, AA130647, F00533, AI192440, AA836552, AA302971, T49633, AI290405, AA668915, N63149, AA668896, AL050306, AC003030, AC006965, AC004491, Z85986, AC007283, AL096703, AC004765, AL078581, AL050318, AC005280, AL022311, AC002477, AL109628, Z84480, U91318, AC007055, AC004815, AC002472, AC006124, AC006071, AC005829, AC005682, AC006079, AC002997, AC004216, AC005932, AC007546, AC007664, AC007536, U63721, Z73963, AF047825, AF196969, AC005764, AC007566, AC004560, AC005632, AC004222, AC004638, AP000696,

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HOELI08	851	958181	1 - 669	15 - 683	AI862922, AI983798, AI817696, AA465702, AI768039, AI831870, and AA459562.
HOEX37	852	708728	1 - 703	15 - 717	H44964, AI570044, AI078541, AI570062, AA733022, H45674, AI084055, W94003, N28018, and AC007285.
HOEU57	853	932562	1 - 818	15 - 832	AW387014, AI831578, AW387023, AW386986, AA862453, AI276148, AI923983, AI925229, AI344497, AI299183, AI343937, AI086925, AW374923, R21305, R18269, AA333257, AI991662, AI093616, W02289, R87814, H08423, AA528079, Z45607, AA455633, W49743, R58057, AI124525, AA767913, Z42086, and R56671.
HOEER75	854	767265	1 - 800	15 - 814	AI989799, AW299570, AI978646, AI638110, AW290948, N67990, AI962847, AW167412, AA706538, N80412, AA961236, AI557808, AI525653, AI557238, AI525669, AI541321, AI541048, AI557258, AI557602, AI541205, AI541353, AI557809, AI535813, AI546829, AI557222, AI535994, AI557543, AI525840, AI541346, AI525656, and AL133617.
HOECI59	855	739426	1 - 640	15 - 654	AI016603, AA884245, AI806142, AI199574, W07522, AI492605, AI767868,



						AW014287, AI143416, AA126482, AW072550, AI377899, AW002034, AI223352, AW418843, AI033261, AI018587, AI760070, AA908231, N80857, AI660406, AW449281, AI479045, AW303620, AW184004, AW195771, AA250993, AI332874, AC003959, and AF086145.
HOECF70	856	573426	1 - 193	15 - 207	AA602457.	
HOEBT89	857	921065	1 - 352	15 - 366	R66475, AI692694, AI677948, N32840, AI187227, T19392, AI499800, H51056, AA169602, AI208443, AW134907, R67315, and AI209123.	
HOACG06	858	954572	1 - 485	15 - 499	AW152166, AA011199, H18839, AI718722, and AA010802.	
HOABY40	859	711510	1 - 540	15 - 554	N62212.	
HOABX26	860	753954	1 - 562	15 - 576	AA065209, AA077377, T32948, AI571240, T08560, R90825, AI033147, AI277382, AI453118, R88021, AA663789, H14060, R87895, AA077707, and AC005071.	
HOABX21	861	531390	1 - 75	15 - 89		
HOABW1 2	862	968797	1 - 387	15 - 401	AI075814.	
HOABG91	863	811156	1 - 221	15 - 235	AB011540, and AB011533.	
HOABF65	864	888203	1 - 284	15 - 298		
HOABD07	865	954060	1 - 358	15 - 372	AI269153.	
HOABA95	866	796063	1 - 405	15 - 419	R31045.	
HOAAW37	867	708718	1 - 330	15 - 344	T97580, and AF143887.	
HOAAW1 1	868	967660	1 - 489	15 - 503	AA525910, and AC004049.	
HOAAW0 2	869	920869	1 - 393	15 - 407	AA284348.	
HOAAV77	870	772512	1 - 398	15 - 412	H84034, and N44965.	
HOAAO86	871	859626	1 - 431	15 - 445	AA662926, AW204080, AA700032, AA514295, N52358, AA621278, AI126468, AA653154, AI986182, AI174766, AA933084, AA829039, AA547947, AI135357, T52475, AW303008, AA601356, AA565484, AI3666993, AI002744, AA630672, AI635819, AA570230, AI630176, AL042756, AW068596, AI920802, N41888, F08230, AW263724, AA507612, AI611960, H93097, T90263, AW002350, AI583255, AI890324, H73230, AA629872, AI628929, AA443390, AC005914, AC002301, AC002395, AC005488, AI109865, AC004801, AC007051, AI034420, AL031846, AC002554, AC007298, AC006057, AC007201, AC008055, AC005668, AL035089, AC005043, AL049569, AC009247, AC004491, AI133246, AI022319, AL009181, AC004216, AF205588, AC003104, AC005482, AP000694, AC007225,	

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HOAAM6 7	872	751947	1 - 292	15 - 306	H50680, and AA779243.
HOAAK71	873	761445	1 - 407	15 - 421	T95206, Z83821, AL020991, and AF068624.
HOAAK11	874	859624	1 - 430	15 - 444	
HOAAI58	875	859643	1 - 679	15 - 693	AW303494, AI039909, AA448710, D31172, D31271, AW195840, D31138, D31112, AA133322, H89975, and AB032978.

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HMUBY20	880	669581	1 - 425	15 - 439	
HMUBV40	881	837969	1 - 420	15 - 434	
HMUBR94	882	793261	1 - 438	15 - 452	AL135377, AA828637, AA084766, AI446336, AA773463, AA984114, AL036037, R20544, AC000025, AC005527, AC005529, AC007227, AL035086, AL035400, AC004859, AC002347, AL008719, AC004531, AL078581, AC006312, AC002563, AC000353, AC004953, AC006111, AP000512, Z95115, AL024498, AC005821,

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HMUBR78	883	955060	1 - 526	15 - 540	AA019047, AI343422, and Z92845.
HMUBQ01	884	918052	1 - 377	15 - 391	
HMUBP74	885	765502	1 - 539	15 - 553	AI432103, N66775, AA555232, AA410788, AA491361, AA228778, AI798449, AA084504, W45274, AI753904, AA324059, AA326603, T93109, AF196779, Z93017, AP000350, Z95116, AF196972, AC004832, AL023575, AL049776, AF024533, AL031311, AL139054, AC003043, AC005089, AC005015, AC005399, AC003029, AL121603, AL034417, AC007934, AC005971, AC005736, AL132777, AF111167, AC007308, AC006057, AP000008, AC000134, AC000052, AL109801, AC002316, AC000159, Z85986, AC007227, AC005088, AC005722, AC004019, AC004890, AC002369, AC008394, AP000704, AC007151, AL049780, U91321, AC005696, AC006064, Z93930, Z82180, Z85987, AC007666, AC006285, AC007878, AP000512, U85195, AC006205, AC003010, AE000658, AC005193, AL031295, AC008072, AC004967, AL022316, AC004030, AF196969, AC006088, AC003684, AC007055, AL031848, Z95331, AC004999, AC006011, AC007051, AC004821, AL035079, and AC005086.
HMUBP38	886	716800	1 - 274	15 - 288	D62503, W31481, W31478, AI031797, AW194041, AW050479, AA737576, AA693819, AA825328, AA860686, AA843163, AA782544, AI026970, AA450017, AA772466, AW152339, AI263677, AI804555, AA347503, AI824356, AI191171, AA993329, AI470261, AI886205, AA632359, AA863458, AI289935, AW132079, AI678407, AI800349, AI623948, AA450366, AA044819, AW188740, AA878533, AI364418, AI874104, AI933937, AA358323, AW131974, AA894788, AW103212, N76132, AA897025, AI915173, AI933628, AI913873, AA860713, N30064, AI579994, AI299561, AA025007, AA781624, R36254, AA934658, AW088795, AW080423, T97261, AI690491, AA614454, AI095864, AW024736, AI016555,

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HMUBN15	887	659543	1 - 452	15 - 466	AA772883.
HMUBN05	888	932057	1 - 455	15 - 469	AF090896.
HMUBM8 9	889	786082	1 - 444	15 - 458	AW302705, AW302659, AI792521, AI792499, AL079734, AI801141, AA468505, AI635440, AL042667, AL042670, T74524, AW192179, AI962030, AL135357, AI053793, AI267269, AI267356, AA603567, AI049709, AA601336, AI267450, AI053688, AA772906, H07953, H82636, AA809546, T41134, AA669238, AA491767, AI733856, AW023111, AI016560, AA659832, AI982884, AI923050, H38769, AI590442, AI754291, Z98044, Z97630, Z84469, AC004764, AL049776, AL035422, AC002470, AC004813, AC009247, AL139054, AC007308, AP000694, AL079304, AF129756, AC005218, AC005874, AF134471, AL133245, AC004382, AL031228, Y10196, AC006511, AF196779, AL049872, AB004907, Z82176, AC008055, AF053356, AC006530, Z86090, AC005081, AL121655, AC002425, AC003962, AC004655, AC005776, AC006509, AP000354, AC005678, U61375, AC006130, AC005520, U07562, AC006050, AP000501, AL031311, U85195, AL023803, AF165926, U91323, AL049697, AE000658, AL009181, AC005323, AC009516, Z98745, AC005071, AC010200, AC002310, AL096761, AF039907, AL135959, AL031276, AL133485, AL021707, AL109798, AC004887, AC007227, AC005015, AL133244, AC006312, AC005924, AC005180, AC006544, AF031078,

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HMUBM8 5	890	784295	1 - 492	15 - 506	AW162314, AW021674, AW265468, N95424, AW438757, AW162332, AI431442, AI755227, AW410844, AW022796, AW327673, AI609992, AI475297, AA112864, AW148821, AL039471, N99245, AW403177, AA568311, AI114494, AA568303, AA631915, AI797998, AA659923, AA618531, AI065031, AA554289, AI076729, AW157128, AW410561, AA507623, AI270280, H96966, AA280886, AI038029, AI144125, AA064983, AA557945, AI567676, AW162762, N72509, AI538404, AA669238, AA568433, AI609107, AI419390, AI568260, AL044701, AI421783, AA847341, AA550837, AW020682, AW277240, AA182577, AW409621, AI819419, AA640305, AI064968, AA074086, AW301712, AW272513, AI859368, AI828721, AA489390, AI224583, AA657392, AI572680, AW246579, AL121039, AW439224, AI702049, AW273201, AW273146, AA101265, AI813920, R99253, AI061313, AI613459, AI281622, AA658890, AL079734, AA225754, AA632355, AI745666,

AI862213, N58334, AI744963, AW238699, AW069769, AA225392, AW274180, AA935827, AA535558, AA533660, AA158023, AI027602, AI590404, AA829693, AA569220, T03928, AI049845, AI569401, AI185856, AI307563, AI174703, AI573009, AI300356, AA157876, AL044966, AW239465, AA772818, AA593168, AI275631, AA610644, AI884404, AI703335, AI423034, AI419419, AL120616, AI049999, AI608751, AA525156, AW008217, AI251024, AA572982, AI283329, AI708175, D88268, AF205588, AC005921, AL135744, AL121658, AC007066, D87008, Z99943, AC005519, Z86061, AC005057, AL049833, AC005839, AL117337, AC007371, AL109809, AL096701, Z84466, AC005913, U62293, AP000152, AC007216, Z93023, D87012, Z83844, AL031311, Z97053, AC005081, AL050321, AC007934, AC004913, Z84480, AC002350, AP000011, AC003688, AC007151, AP000211, AP000133, AC007308, AL034429, AL109623, AC007546, AE000659, AL008582, AL022238, AC004231, U91326, AC007676, AF109907, Z84469, AC005288, AL022162, AP000703, AE000661, AL035422, U85195, AB023050, AF196779, AE000658, AC005084, AC005696, AC007052, AC005920, AL022165, Z98946, AC005500, AC004673, AC007298, U89335, AC002115, AC004383, AC004841, AL049843, AL049759, AF124731, AC005969, AF118808, AC002563, AC005291, AL031733, AL080243, Z84487, AC007899, AC000025, AP000044, AP000112, AC005529, AC004890, AL133163, AC005527, Z93241, AJ006345, AL132777, AC007686, AC005484, AC002055, AC007240, U95742, AC016026, AC003110, AC002369, AL133245, AC004967, AL031985, AF047825, AC007845, AC007055, AL049830, AL133312, AC003051, AC007637, AC004929, AC004645, AL049872, AC006449, AC003043, AC015853, AC004106, Z98200, AC006121, AC002544, AL118497, AC008134, AC006004, AC005594, AL022315, Z98742, AC000111, AC005011, AL078621, Z82190, AC002425, AL139054, AF023268, AF134726, AC006441, AC009501, AL031589, AL049569, AF207550, AL031670, AL035398, AC005261, AC009247, AC004797, AC005808, AF055066, AC006317, AL022333, AC005488, AC006166, AC006006, AC005102, AP000555, AC012627, AL109963, AL020997, AC005822, AC007666, AC008928, AC004139, AL121652, U78027, AC004974, AC004765, AC004686, AC005666, AC005736, AC004820, AC004491, AL109758, AF124523, Z84474, Z97056, AC005778, AC005277, AC000003, AC004506, AC002470, AP001052, AC005399, AC004019, AC006600, AL078639, AC003982, AF001550, AC005971, AC006111, AC007226, AL078584, U85199, AL049576, AL034561, AC006211, AC006511, AC004668, AC002133, Z84476, AC005914, AL023803, AC016025, AP000511, AC004887,					
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HMUBM2 3	891	675296	1 - 361	15 - 375	R51236, R45099, Z40109, and AF107403.
HMUBM2 1	892	861218	1 - 513	15 - 527	
HMUBM0 1	893	916291	1 - 541	15 - 555	AF039239, AA156352, AI928298, and AC004596.
HMUBL79	894	774904	1 - 279	15 - 293	
HMUBL25	895	678011	1 - 735	15 - 749	T83448, and AC004051.
HMUBI26	896	424764	1 - 534	15 - 548	R11938, and R17505.
HMUBH84	897	782971	1 - 467	15 - 481	AI300542, W91888, N63093, AL117338, AL049569, AL031687, AL035209, AP000697, AC004099, AL035415, AL008718, AC005089, and AC002563.
HMUBC76	898	769968	1 - 466	15 - 480	H53236.
HMUBA75	899	767192	1 - 363	15 - 377	AC007250.
HMUBA61	900	741710	1 - 429	15 - 443	AP000365, and AP000547.
HMUA71	901	772958	1 - 350	15 - 364	AA160854, R71813, R71760, R48639, N42220, AW247533, R50575, AW170393, AA083908, AA313213, AA455790, AI372424, AI700503, H30234, AI807620, AI149104, R85186, H74174, AA371702, H67210, R90881, AI148673, R70330, AA380748, W86716, AI421626, R80075, R35880, H30476, W31820, AA099322, AI014871, AA323925, H04088, AI951537, AI498026, AW027328, R70448, AC006165, AB023051, AP000512, AF085357, AF089750, AF145044, U90435, U60976, and U60977.
HMUA85	902	783543	1 - 313	15 - 327	AA027138, AI752271, AI880296, AI752272, and D80011.
HFOZC29	903	923288	1 - 555	15 - 569	AI095431, AI571923, AW261883, AI200605, AA482065, AI200699, AI017296, AI923202, AW015684, AA767648, AA883935, AA677666, AI573221, AI033576, AI126442, AI369853, AI249160, AI142443, AW264134, AA806683, AI092218, AA858007, W94283, AI339695, AI262289, AI076383, AI311852, AI910100, H46722, W85678, W74408, AA631052, AA918365, AI301845, AA604026, W72883,

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HFOZA47	904	909372	1 - 303	15 - 317	T99977, AA386007, AW419200, AI301419, T99978, AA813111, and AL133243.
HFOYW76	905	769894	1 - 387	15 - 401	Z43100, R23391, R18897, and AA775801.
HFOYV08	906	959038	1 - 503	15 - 517	AI885037, AW005574, AI127653, AI471784, AW002166, AI652199, AA775784, AA398384, AA525786, C21259, and Z98048.
HFOYSS8	907	735816	1 - 267	15 - 281	AA464919, AI360067, and AI563967.
HFOYN65	908	747740	1 - 403	15 - 417	R42824, AI418414, AI094617, AI159874, AA614150, AI420613, AI082558,

						AI478270, AA928271, AA477739, H29542, AW297075, F35711, AW292053, Z39149, AW362068, F25020, and AI597841.
HFOYN01	909	854780	1 - 446	15 - 460		AA188606, and AL109710.
HFOYM48	910	721455	1 - 461	15 - 475		N69806, AI692502, AI077479, AA811249, N69787, and AC0000076.
HFOYL33	911	702209	1 - 593	15 - 607		W03664, and AW070784.
HFOYK21	912	670653	1 - 852	15 - 866		AA428559, AA429496, and AA909127.
HFOYK02	913	919458	1 - 475	15 - 489		W38502, and W21229.
HFOYJ30	914	932485	1 - 669	15 - 683		W67514, AI655409, AW051595, AI799668, AI400464, AA563735, AI183528, AI354914, AA652158, AI337235, AA652105, AA961057, AA772564, AI093875, AA889803, AA442063, AI652462, H17951, AA442166, W68127, H12516, AI365333, N95071, AA861656, AA939316, R71444, AA917342, AA487907, R81789, D62541, R71096, AI355106, F13621, AI277031, Z38139, AA773369, AI419837, H12464, C18326, AA767156, and AF116827.
HFOYH01	915	916055	1 - 555	15 - 569		AI733400, AI392911, AA669057, AI522044, AW293639, AI261721, AI791812, AI792235, AA948371, R82728, and AI017805.
HFOYG88	916	494875	1 - 794	15 - 808		W81024, AA040397, AI806528, AI626098, AI474320, W81060, AW181963, and N92485.
HFOYG86	917	949496	1 - 549	15 - 563		AI089319, AA495807, AI122079, AI682875, and AA626188.
HFOYC08	918	958975	1 - 627	15 - 641		AI939308, AI089885, AI674951, and AW452881.
HFOYA17	919	662642	1 - 334	15 - 348		H85252, and Z59473.
HFOXW67	920	494854	1 - 497	15 - 511		R59304, Z41276, and F01353.
HFOXV94	921	794175	1 - 494	15 - 508		AA224103, and AC005328.
HFOXIT74	922	875383	1 - 522	15 - 536		AA203672, AA521316, AW025339, AI971502, AA833669, N71094, AA832189, and AC003029.
HFOXT35	923	707088	1 - 506	15 - 520		
HFOXSA42	924	713514	1 - 462	15 - 476		
HFOXO57	925	928171	1 - 493	15 - 507		N62077, AW408398, R14585, W44378, R52298, H29068, AA258983, R14764, R60391, and AL022165.
HFOXO33	926	702212	1 - 555	15 - 569		R00471, F22586, AI473631, AA773289, AI758435, AI471914, F34093, AA397821, H48670, AA251356, AA298788, F27108, AI798493, T06210, AW439008, AA130501, AW245331, AA737039, AA523695, AI366902, AA804866, AA523812, AI865375, AW021619, AI054339, AC006509, AC011456, AC002504, Z98750, AC006960, AC004526, AP000466, Z83844, AF048729, AC005261, AC007695, AC006285, AC003043, AC003010, AC004844, AC004067, AC005102, AC004841,

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HFOXM53	927	587972	1 - 546	15 - 560	T95196.
HFOX L88	928	909839	1 - 412	15 - 426	AA077980, AA010232, AA077893, AA149376, AA029227, AA077669, AA077229, AW386712, AW386708, AA076983, AA076893, R53155, AB011110, and AC004084.
HFOXK96	929	732057	1 - 549	15 - 563	N95619, AI522016, AW418929, AI739123, AI589262, W81467, AA679593, AI358082, AI968962, H29504, W81348, AI802044, AA860722, AI299531, AA861993, AI240698, AW293669, AA946852, AI538012, AI872899, R40786, AA703596, AA426331, N45617, AC004918, and AL049792.
HFOXK42	930	587960	1 - 400	15 - 414	AI369443, H40699, H38679, TI0030, AI359972, AB032985, and AC006487.
HFOX F91	931	790103	1 - 640	15 - 654	AW299538, AI700655, AA542898, AI201894, AW002387, AW299893, AW135284, N48798, AI953361, AI088991, AI381950, AI239629, AI206950, AI217419, AI361123, AI687555, N62233, AI669545, AI700194, W40211, AI537667,

						AW118331, AI569799, AI300682, H22991, AI686217, R45601, W45433, AI867656, AA402541, AA766044, AW156969, AW162279, AW157242, AW301566, and AL034379.
HFOXF42	932	854797	1 - 410	15 - 424		F00438, AB029032, and AL137384.
HFOXD78	933	856499	1 - 320	15 - 334		W00471, AW363484, H05198, F11931, T66107, and AL049471.
HFOXB33	934	701719	1 - 617	15 - 631		AA070455, and AL049775.
HFOXBB26	935	681593	1 - 455	15 - 469		AA159285.
HFOXA62	936	743466	1 - 435	15 - 449		T86297.
HFIZP86	937	785341	1 - 409	15 - 423		AA418200, AI280402, and AI350784.
HFIZB62	938	743122	1 - 693	15 - 707		AA131059.
HFIFYX08	939	958977	1 - 443	15 - 457		AA605145, AA702116, AA708181, and AL096678.
HFIFYW79	940	858618	1 - 652	15 - 666		R56716, AW075513, AW002149, H39705, H28690, F11371, AA768949, AA384664, AI337892, AI057281, AI458151, AI570407, AW134516, AI350058, AI470179, AI215812, AA854471, R26470, AA251002, AA573328, AI216845, AI200607, AI984370, AA411536, AI298938, AI818816, AW083096, AI300345, W92747, AI147626, AI948774, AI262533, AA725905, AA442075, AI565962, AI301560, N52183, AA935514, AW149691, AI194002, AI291200, AI304886, AI953743, AW270856, R63834, W35349, AW340470, AI765586, AI298116, and AA292171.
HFIFYS11	941	966702	1 - 467	15 - 481		N58560.
HFIFYN50	942	724175	1 - 538	15 - 552		AI458879, AA463632, AA496023, AI168467, AA778374, AI580056, AI056137, AI269041, and AI360731.
HFIFYJ92	943	791305	1 - 462	15 - 476		H96503, AI629004, AI436691, AW264067, AI796727, AW341625, N20097, H15455, N24619, AI949464, D62682, D63004, T65294, N23339, N94925, AA099864, AI095277, F09804, R40594, R60524, and N59847.
HFIFYA08	944	962212	1 - 536	15 - 550		AA458753, AI870866, W72843, AA772868, AI130854, AI083630, AA130359, AA056018, AA332556, AI199995, AA469081, AA661635, AI183475, AA457490, AA931966, W67545, W67527, W81565, AA826675, T12258, W76412, AA989066, W81612, AA630878, AI243042, AA027306, and AA056067.
HFIXZ95	945	915703	1 - 466	15 - 480		AA126477, AW299841, AI742474, AI672617, AW001691, AW008181, R76817, R43164, AI990788, R22570, R28278, H95582, H95556, R75986, R92020, AI983816, and AC006055.
HFIXZ19	946	683033	1 - 600	15 - 614		AA053791, AI755151, AI633860, AL046181, AA205728, AA211578, AA204943, AI635990, AI830932, AI949778, AI949366, AI634857, AI823973, AI423292, AI627291, AI418579, AI890410, AA836883, AI480105, AI669422, AI095121,

					AI057276, AI890178, AA205729, AI200542, AW078637, AA166692, AI669371, AI32344, AI217515, AI359771, AI378663, AA224514, AI554321, AI990118, AA630767, AA410286, AW264316, AW206186, AI669078, AI923406, AA468567, AA552010, AA121794, AI754877, N51861, AI823545, AI650324, AA099437, AI356067, AI038127, AW129642, AI273625, AI619475, AI767029, AI827395, AI022904, AI174419, AI765993, AI091669, AA165151, AA961611, AA780769, AW020059, AA169647, N90277, AA035739, AA788579, AA169822, AI830936, AA452593, AI002825, AA706408, AI583400, AI59181, AW023827, AA205712, DI2323, AI367552, DI1546, AI571708, AA807016, AW382024, AW382030, AW382019, DI1548, AI349108, AA027830, AL045597, AI564852, AI914393, W35293, AW381974, AA746978, AW393593, AI685993, AA678665, AI392778, D54048, F37948, R44031, AI695043, AW382056, AI619567, AA431088, AA664873, AW381977, AA860448, F25971, AA760888, AI630054, AA214120, F37021, HI1493, CI5312, AI571876, AA216657, AA779052, AI521854, Z28566, AA436971, AA502233, AI300701, AI872541, AA256938, W38598, HI3644, AA224488, AI567021, Z38535, F01833, AI245064, AA431553, AW382004, H43488, AA884498, R57005, H39529, AA912371, AF131807, Z99716, and AL008721.
HFIXR93	947	894013	1 - 572	15 - 586	N25971, N29465, AW410261, and AI435020.
HFIXR68	948	752858	1 - 805	15 - 819	RI1083, and AA393561.
HFIXP31	949	697759	1 - 453	15 - 467	AA227552, AI080405, AA227929, AI972469, and U69274.
HFIXP04	950	839910	1 - 549	15 - 563	AA883171.
HFIXI53	951	489122	1 - 409	15 - 423	T72754, and AL049713.
HFIXB77	952	772116	1 - 501	15 - 515	R82686, and HI9381.
HFIVS81	953	387591	1 - 230	15 - 244	AI420574, AW237773, AI375677, AI244780, AA528140, AI624970, AI624952, HI5695, and Z39216.
HFIVS21	954	855131	1 - 267	15 - 281	AA578341.
HFIVS08	955	959272	1 - 390	15 - 404	CO1483, and AC007032.
HFUJZ63	956	745033	1 - 554	15 - 568	AI672293, N59774, AW014476, AI091467, AI740712, AI306424, AI215771, AI652127, AA683496, AA868095, AA436090, AI379664, AI419802, and AA435990.
HFUJY49	957	855133	1 - 394	15 - 408	AA501785, T74524, AW274349, AW303196, AW301350, AL049539, AP000555, AP000223, and AP000086.
HFUJY58	958	735350	1 - 752	15 - 766	N22766, AI094120, W94915, AI140008, AI339057, W91968, AI378174, AA628702, AA628693, AI080429, AI168313, H97684, AI868702, AI886569, and AA236390.

HFIUV18	959	787095	1 - 499	15 - 513	H29983, AW298799, T86660, T79509, AA400497, AA400589, T96108, H54131, R98500, R98518, T80762, and AA359852.
HFIUM33	960	702319	1 - 359	15 - 373	AA634147, AC006014, AC005488, AP000696, AC007226, AL109952, U80017, AL031985, Z95114, AC005578, Z85987, AL008715, AL031297, AL049576, AP000088, AC004765, AC002470, AC007899, Z97054, AL049843, AL022721, AC005081, AP000689, AC005924, AC003010, AC004002, AC004662, AC007934, AC005399, D87675, AC004966, Z95116, AL133245, Z49236, AC004033, AC005520, AC005368, AC007537, AP000047, AC004941, AC007285, AC005280, AL109628, AC004890, AL022313, AC002310, AL078475, AP000031, AC004019, AL031295, AC007731, AC005874, AF134471, AL022163, AC005500, AL121603, Z86090, AC005004, AC007842, AC004668, AL132712, AC005324, AL021918, AP000553, AC002425, AL031311, AC004985, AL049869, AC016026, AB023050, AC005082, AC005666, AC005527, AF109907, AF030876, AC007227, AC007536, Y07848, AC004526, AL024498, AC000025, AP000512, AC004858, AJ251973, AC004263, AC004531, AC005971, AC005409, AL049643, AP000115, AP000116, AP000049, AL109798, AC005881, AC003041, AC007358, AL021391, AL031670, AL021707, AC006026, AB003151, AC004686, AL096791, AC004228, Z81364, AL078581, AC002395, AC005736, AL049872, AC007845, AP000311, U95740, AC004491, AP000251, AC005598, AC004132, AC002546, AC009247, AL050332, Z99127, AC003665, AC004895, Z98742, AC003109, AC005730, AC002544, Y10196, AC002477, AF031078, AL133445, U95742, AL049697, AC005899, AC005841, AL034379, AC005529, AC016025, AF181896, AL132987, AC002059, AF129756, AL024474, AC005911, AC002996, AC005046, AC004067, AP000211, AP000133, AP000030, AC000120, AC006511, AC002350, U91323, AC003688, AF088219, AC004988, AL049776, AL117337, AL049759, AC005668, AC005839, AL009179, AC000134, AC006111, AC006211, AL049795, AC006597, AF196779, AD000864, AC007546, AC005233, AC005746, AL080243, AC004841, and AL034418.
HFIUH65	961	747836	1 - 517	15 - 531	AI608715, AI422803, AI432163, W63666, H81684, C05948, W37721, AI493291, AI356167, H84536, AA988027, AA401876, AA872375, AA932978, H84219, AA868682, and H81685.
HFIUD47	962	720254	1 - 570	15 - 584	W07634, AA194651, W94182, AA133411, and W07638.
HFIUH46	963	718078	1 - 659	15 - 673	H83995, R84314, AA813574, T05535, and AL915423.
HFIJG36	964	707883	1 - 733	15 - 747	AA001287.
HFIJG20	965	669580	1 - 421	15 - 435	R05639.



HFJUF58	966	735927	1 - 659	15 - 673	AA242859, AA252126, AI693548, H99361, AL049780, and AC006530.
HFJUZ92	967	494044	1 - 461	15 - 475	AA493255, and AL049781.
HFJUU85	968	793332	1 - 789	15 - 803	AA486519, N75864, AA282436, AI311373, AA987662, AW378576, AA258100, D20734, AA398828, AI340090, AI806551, AI827300, AA322510, AW167535, AA486153, AI580840, AA307592, AI300646, AI365620, R63162, AW190730, N80417, AA074806, AI380183, AI807739, AI683461, AI817082, AI798145, AI423017, AI056695, AI590919, AI127969, AW055144, AA648622, AI860727, AI571273, AW173640, AW305299, AI445732, AI283109, AA173927, H13876, AA486091, AI692781, AI692782, AI475726, AI567671, AW368584, AW339198, AA598864, D57989, AA773684, AI347553, AW304900, AI310482, AW103494, AA135489, AA300795, AW377765, AA424654, W53016, AI950989, AA150819, AI024706, AA360720, AI751636, AI753529, AI950558, AA604851, AA579895, AA931400, AW129397, N39046, N35027, AI355248, AI805101, AA424557, H07110, AI860066, AW192391, AI469260, N67995, AA223733, AI863857, AI302384, AI355266, AI299079, AI148180, AI003944, AI934032, AI830970, N70657, AI340222, AW402035, AA554911, AA565608, AL080212, and U07795.
HFJUR63	969	744994	1 - 732	15 - 746	R60665, H06153, and R14432.
HFJUL37	970	561375	1 - 337	15 - 351	AI185219, Z99396, AL038837, AL037051, AL036725, AL036418, AA631969, AL039074, AW392670, AL036858, AL036924, AW372827, AL039564, AL039085, AL038509, AL039156, AL039108, AL039109, AL039128, AW384394, AL119497, AW363220, AL037094, AL039659, AL038531, AL036196, AL036190, AL119335, AL119443, AL037639, AL039625, AL039648, AL119319, AL045337, U46351, AL119457, AL036767, AL037082, U46350, AL037526, U46341, AL119496, AL119324, AL119484, AL119363, AL119391, AL119483, AL119522, AL039678, AL039629, AL119341, AL119355, AL039423, U46349, AL036238, AL119396, AL038447, AL039150, AL040992, AL134528, AL042909, AL042450, AL039386, U46346, AL134524, AL037077, AL036268, U46347, AL119418, AL042614, AL119444, AL037085, AL038520, AL037726, AL119439, AL036998, AL036733, AL042975, AL039410, AL037615, AL038851, AL134533, AL037205, U46345, AL134518, AL042965, AL134531, AL119399, AL037027, AL036719, AL037178, AL042984, AL042970, AL043029, AL042551, AL134538, AL119488, AL036679, AL134542, AL036191, AL042544, AL043019, AL042542, AL036765, AL043003, AL037054, AL119464, AL036774, AL037021, AL036836, AL036999, AL036886, AL036158, AC006001, AR060234, AR066494, A81671, AR023813, AR069079, AR064707, AR054110, and AB026436.

HFIIK75	971	767222	1 - 845	15 - 859	AI458975, AW296300, R44335, AW452866, AI276446, AI700567, R40979, AI264364, AA884637, AA257160, Z17361, and AA257067.
HFIIK32	972	424259	1 - 396	15 - 410	R81615.
HFIIK07	973	953034	1 - 481	15 - 495	AI630872.
HFII14	974	839523	1 - 694	15 - 708	AI888852, AL046620, AL044458, AW085811, AI732327, AA780914, AA618132, AI679294, AI679871, AA525818, AA524604, AA640305, AA523718, AI828721, AI282322, AL121039, AI702049, AI732720, AI344906, AA313025, AI567676, AI285651, AA493245, AA054283, AA631915, AA577706, N27362, AA515727, AI984168, AA664963, AA935827, AW072963, AW265006, AA482682, AI049845, AI926102, AA493546, AI734075, AI246541, AI734076, AA831913, AI114494, AW238242, AI275631, AI570067, AW157128, AI813920, AI572680, AA554289, AI242236, N49298, AI733523, AI889177, AA507623, AI538404, AA618531, AI038029, AW085626, AA593168, AI174827, AW327673, AA601336, AI860423, AI609992, AA601376, AL044701, AA834891, AW419201, AI734119, AA523719, AI003068, AA404619, AI521525, W44797, AW268793, AW265468, AI434103, AA602939, AA493464, AA425283, AW301483, AA595508, AW021674, AA728954, AA723282, AA584360, AI753092, AA557945, AI889236, AI281622, AA676462, AI002950, AA629668, AA834799, AI312614, AI826857, AI350189, AA167656, AA493808, AI064968, AW057760, AI039257, H29593, AA847341, AA728952, R92703, AA299490, AA526542, AA491941, AI744890, AI884404, AA515728, AA811451, AW410844, AL118843, AA558488, AI342863, AI061158, AW339619, R61887, AA729004, AI745666, AA421536, AI148840, AW103990, AA197089, AA636077, AI003391, AA489390, AI889995, AI791720, AI791408, AP000512, AL009181, AC005081, AC005911, AC004491, AC004765, U62317, AC005231, AC004801, AB017602, AD000092, AL031666, AL117258, AC004967, AC006271, AF003626, AL049694, AL136504, AL020997, AC004000, AL031133, AC002310, AC005015, AC007637, U47924, AC004671, AL022323, AC004834, AL136295, AC005800, AC006449, AC005412, AC009247, AL049569, AC004752, AL133245, AL031311, AF111169, AC005046, AC005887, Z95116, AL080243, Z93241, AL031668, AP000692, AC005004, AC004805, AC005755, AL008582, AF053356, AF109907, AC002565, AL023575, AL031602, AC005088, AL109628, AP000356, AC007151, AP000211, AP000133, AL008719, AC004253, AF038458, AC004854, AC007934, AF0003529, AC007030, AC005041, AL035423, AC007226, AC002477, AL096701, AC007666, AF111168, AC006211, AC004659, AF047825, AF067844, AL022316, AL031680, AL022326, AF064861, AC007707, AC005562, AB023051,

					AC016025, AP000131, Z99716, AC006450, AC005619, AC006080, AC004799, AL031733, AC005722, AL021395, AC006064, AC005089, AL031431, AC003007, AC004031, AC005881, AC002314, AP000503, AC005913, AC000353, AL031730, AC007055, AC004678, AC005519, AL035413, AC003006, AL133448, AC002425, AC005971, AC002404, AL035460, AC005406, AC003956, AL109758, AP000555, Z92542, AP000501, AC005067, AL031589, AL133163, AL049757, AL031846, AC008044, AF111167, AC005839, AC005102, AF165926, AC006285, AC005180, AC004382, AP000350, AC006261, AP000688, AJ003147, AC005696, AF134726, AL139054, L78833, AL050348, AC005808, AC002126, Z85986, AL049776, AL049780, AC007227, Z86090, AL031657, AL049759, AC006013, AC004703, Z98044, AC002381, AC006160, AC005225, AC002470, AC006011, AL031291, AC006006, AC005914, AC005280, AL034423, AL034429, AC004686, AC002400, AC004216, AC005258, AC003029, AC004983, AP000346, AC005537, AP000152, AL050321, AC005736, AC000003, AP000510, AC005527, AL034555, AJ246003, Z95114, AC007774, AL008726, AC006101, AL022311, AP000247, AC004560, AL121657, AL035587, AC005484, AC005480, AC007688, AC004887, AC004605, AL034451, AC000039, AC005632, AC007536, AL049745, U91328, AC002554, AC002073, AL050307, AC005921, AC005566, AC007011, AC003950, AC010077, AC002558, AC007216, AC004257, AC008009, AP000553, AL034417, AP000511, Z98051, AC006057, AC007371, AC006312, AC007450, AC004662, Z98742, AP000008, AC004263, AC007050, AL049576, AC004876, AC003982, AP000466, AC006205, AC003108, AL050341, AB000882, AC005245, AL121825, U52112, AC004033, AJ011930, AC004477, AC004849, AB023048, AP000500, AC004526, AC004643, AC006115, AL022302, and AC008372.
HFHW91	975	907618	1 - 515	15 - 529	AI743173, AA909302, AA447375, AI470475, and AI066540.
HFHW16	976	858594	1 - 659	15 - 673	H42111, and AF142099.
HFHW11	977	947856	1 - 269	15 - 283	AA828809, and AA828563.
HFHV56	978	470954	1 - 687	15 - 701	AA160654.
HFHW76	979	769948	1 - 347	15 - 361	AW055256, T59260, H67680, AI002890, H68002, AC004883, and AC005412.
HFHS86	980	785419	1 - 344	15 - 358	H89010, AW021356, AW023646, and AL035694.
HFHR78	981	773512	1 - 457	15 - 471	H84598, AA777769, AA682587, AI090880, and AI862169.
HFHN35	982	707075	1 - 895	15 - 909	N54488, H47963, AA708179, H56418, R92521, H83039, and H60100.
HFHK29	983	855174	1 - 834	15 - 848	AW082328, AA056697, AA058386, AI582825, AW376061, AW204615, AA847499, AI923052, AI754105, AI755214, AI754567, AI278972, AA630854, AI962030, AW328202, AA584484, AA904211, AA503019, AA410788, T74524, AA704393,

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HFIFH53	984	728259	1 - 560	15 - 574	R65697, R65696, AC007688, AF165926, AL022165, AC005702, and AC005519.
HFIFD20	985	669731	1 - 496	15 - 510	T55518, AI762631, and AB002380.
HFIDL68	986	928475	1 - 516	15 - 530	AI375172.
HFIDL06	987	837524	1 - 599	15 - 613	AI141922, W51817, AA515912, AI925832, AA614027, and AL133051.
HFIBK83	988	939556	1 - 490	15 - 504	RI5292, AW339546, Z42543, AA251688, Z44339, W60548, F06562, AW377760, and AA011443.
HFIAIX78	989	773445	1 - 280	15 - 294	
HFIAS49	990	722728	1 - 599	15 - 613	N35671, AI301181, and AC007093.
HFIAL66	991	587837	1 - 503	15 - 517	AW172309, and N42465.
HCOKA10	992	907080	1 - 759	15 - 773	AW327294, F31091, AA528669, AA505384, AW328419, AW328418, AW419243, AA187998, AA640483, F31092, AA420717, AI348852, W81029, AA482925, AI879569, AA946918, AA314600, AA825612, AA808869, W45176, AA316648, AA651658, AI735276, W52650, AA534263, AA314556, AA417254, AI342431, AA622408, AA181138, AA506547, W68664, AA635583, AA991834, AA187537, AA128015, W96306, AA505394, AA186606, AA524595, AI336250, AA862109, N90275, AA187128, AA737195, AA659642, AI879186, AA307087, AA991775, AA579430, AA643777, F32467, AA654628, F33074, AW082068, AA484856, AA653801, AA469168, AA420763, AI090379, AA421550, AA469285, AA775298, N78682, AA225075, AA314013, AI735264, C15999, AI004885, AI185905, AA155975, AA541346, AW006688, AA838376, AA507479, AA315116, AA147815, AW440264, F25989, AA528681, AI718105, AI185191, AI830011, AI074436, AI193986, AA483568, AA844667, F30622, AI598223, AI431978, AA157591, AW340929, AI718714, AA147943, AA960763, AI140252, AI131544, AA659113, C14408, F28423, AI193088, AI749326, C14506, AA181285, C14409, AI302400, AI570974, AI936281, AA229654, AA229788, AA302294, AI982992, F31208, AA935155, AI193847, H46476, AA838474, F20187, AA492052, AI609502, AI709111, AA469365, F32353, AA608589, AA643956, AA961534, AA226596, AI973135, AA128058, AA829205, AA501744, AW276969, AI721218, AI924736,

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HCDEL02	993	920831	1 - 279	15 - 293	AI300611, and AI700656.
HCDDZ69	994	522220	1 - 329	15 - 343	AA631784, T53408, AA427747, AA904211, AI473671, AA721530, AA721523, AA604831, AA017583, AA731361, R94436, AW080215, AW054936, AC002310, AC006312, AC005924, AC005519, AC004883, AP000501, U80017, AC009399, AP000359, AC004796, AL021154, AC004448, AC012384, AC005088, AC002365, AC003110, AC005722, AC005844, AC007666, AC005280, AP000555, AF024533, AC004983, AC003029, AC005899, AC005740, AL049759, AL022316, Z93023, AP000692, AL133353, AC005209, AB023049, AP000008, AC007308, AL031666, AL022318, AL023575, AC009247, AC004895, AC003101, AC002477, AC005932, AC005482, AC006057, AC004019, AC007066, Z99943, AC002432, AC006071, AC007934, AC003042, AL049709, AL022163, AC003690, AC007298, AC006084, and AC002301.
HCDDY54	995	529265	1 - 344	15 - 358	

HCDDO80	996	778563	1 - 421	15 - 435	AI732570, AA134460, AI871333, AI744693, AI610347, and AI563999.
HCDCD64	997	863415	1 - 389	15 - 403	N31472, N29138, AI880074, and H85753.
HCDBW41	998	712648	1 - 463	15 - 477	R43504, R59580, Z39594, T15652, F01654, and Z95118.
HCDBO86	999	784617	1 - 672	15 - 686	W93682, AW242652, AW173253, AI139152, AI553736, AI290544, N49727, N52656, Z41613, AI184287, D61097, AI918560, AA258656, and AF028333.
HCDAO39	1000	704504	1 - 264	15 - 278	AA188026.
HCDA68	1001	753814	1 - 617	15 - 631	R95822, and AA019299.
HBSAP57	1002	531874	1 - 631	15 - 645	AI500721, AA534064, AA829251, AI380617, AW304580, AI826761, AW020150, AA714110, AI560085, F35374, AI278972, AA904211, AW303196, AL042735, AW301350, AA282951, AW410354, AL079734, AW151541, AA515728, T50676, N23913, AA706495, AA983673, AA086318, AA613627, AI440117, AA515048, AA503298, AI962030, AI436433, AI683131, AA833875, AA833896, AI133083, AI249365, AI049709, AI279417, AI354333, AI755214, AW188427, T74524, AW237905, AA704393, AA456924, AI744199, AI754567, AI792521, AA526542, AW069769, AI754105, AA535216, AI053398, W96522, AA284247, AI114557, AI469577, H63660, AI565084, AI950963, AI114733, AI133552, AI216990, AL046746, AL041894, AA809546, AA225406, AI587349, AI355007, AI681962, AI186438, AA659832, AI192440, AI923052, AA420801, AW020094, AA502532, AA719524, AW272294, AA975779, AW271904, AW019964, H82636, AI343169, H73561, AW081303, AL048135, AW157731, AI801505, AI491765, F35097, AA654013, AW419389, AW021399, AI609972, AI859438, AA470578, AA524616, AI362442, AI499954, AI521525, AI635028, AW243793, AC005746, AC005288, AP001060, AC005015, AI009610, AC005940, AL021453, AC007421, AP000501, AC005409, AC005412, Z99714, AC002565, AC010205, Z95331, AC004805, AC007376, AL049776, AC007227, AC005378, AL008627, AC006160, AC004242, AC007546, AL049869, AL139054, Z84480, AC004895, AC002375, AC006040, AC005747, AL022163, AC002302, AC007263, AC005212, AP000696, AB026898, AC005089, AL022165, AC005837, AC003101, AC004886, Z97054, U47924, AC008154, AL031587, AL022336, AC004134, AL117355, AC002430, AC005261, AC007014, AP000704, AL031281, AC003692, AC007384, AF053356, AC006538, AP000086, AC005828, AC004019, AC007934, AC006449, AC005041, AC005399, AP000555, AL022721, AC005531, AC005037, AF111167, AL022302, AL049766, AP000131, AP000209, AC007919, AP000553, AL117354, U91326, AC005722, AC007676, AC002299, AC005304, AC006468, AL109984, AP000694, AC007225, AL133245, AC011311, AC005071, Z95114, AC002551, Z99716, AC007051,



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HBCKF23	1003	675613	1 - 505	15 - 519	AA429449, AA428527, AA995146, and AI041267.
HB CGD25	1004	677689	1 - 462	15 - 476	H40377, H51703, T70759, T69773, and H40323.
HAOAE95	1005	795674	1 - 304	15 - 318	T39786, T39845, and AL034417.
HAOAD27	1006	848729	1 - 472	15 - 486	AI123100, AW195077, and AL096776.
HANKG10	1007	963926	1 - 456	15 - 470	AI373332, AW243457, AW235081, AA748692, and AW362939.
HANKB13	1008	827062	1 - 423	15 - 437	AA278465, AI979103, and AI908300.
HAMAC79	1009	872774	1 - 1081	15 - 1095	AI358042, AI874151, AL039730, AI400725, F37364, AI887268, AL080011, AW302924, AW193203, AW088899, AW409775, AI433206, AA807088, AA864562, AI355008, AI537677, AI434242, AI345347, AI918554, H89138, AI859464, AI800464, AW411235, AL038445, AI251221, AA911767, AW168503, AL046926, AI521386, AL119863, AI582483, AI886594, AW022682, AI829990, AI922577, AW089006, AA464646, AI954422, AL036638, AI612015, AW161579, AW168031,

AI620093, AW058233, AI573026, AL120853, AI919593, AI590423, AA100772, AI539153, AI933992, AL042382, AI345224, AA127565, AL120526, AI917959, AI311892, AI697324, AA643261, AI280670, AA603709, AI344928, AI952064, AL038069, AA853213, AW021373, AI680498, AI698401, AI580674, AA853539, AI659795, AL048871, AI470293, AI570966, AW089932, AI344933, AI554343, AI916419, AI677797, AW238730, AI537617, AI494201, AW076127, AI920782, AL119791, AL041150, AI335449, AL038076, AW265004, AI927755, AI963040, AI582871, W81248, AA761557, AI573093, AW029401, AA420758, AI537837, AL046463, AI241819, AI874166, AI340533, AW083804, AL038715, AI955945, AI334445, AI336575, AI696969, AW059828, AI073952, AI633477, AW078680, AW004886, AW082623, AI312399, AI648502, AW238688, AI802240, AI866127, AI335426, AL110306, AI348777, AW410969, AA572758, AI889168, AI671661, AI690663, AI929108, AL036772, AI500039, AW162194, AW305233, AI678355, AW074869, AI612014, AL037041, AI471361, AI866100, AW160376, AI343059, AI284509, AW193134, AI669639, AI866082, AI280661, AA493647, AL042365, AI349933, AA420722, AW268261, AI345608, AI285586, AI446124, AI923989, AI348897, D50977, AI174591, AI345251, AW020710, AI419650, AW081255, AI689420, AW301300, AI348847, AI251830, AI917963, AW193872, R36271, AI344819, AI862220, AI648567, AA291456, AW029579, AI434833, AL040241, AW075207, AA848053, AI345253, AW020397, AI312152, AI950688, AI343037, AW269097, AI345677, AA938383, AI696611, AI446373, AW075084, AW087385, AI523806, AW301409, AL047387, AI932458, AI473451, AI340603, AI919345, AI290153, AW151714, AW088903, AI364788, AW130863, AW129230, AI830030, AW084097, AI307543, AI249877, AI345370, AI932949, AI799234, AI345527, AW021717, AI289542, AI348854, AI817430, AI242736, AI699056, AI446092, AI307569, AI345471, AI344935, AI805638, AI334820, AI365256, AI366549, AI366992, AI636719, AI313320, AW190286, AI336495, AI478123, AI453487, AW085786, AW081034, AI539771, AL039086, AI866608, AI472536, AI307520, AL043981, AI805688, AI611743, AI340664, AI590686, AL040207, AI368816, AA830821, AW191844, AI309431, AI888621, AI348917, L78810, AL035407, AC005091, AC006013, AC004686, AC002454, AC004383, AC004878, AL022147, U62317, AL137705, AC004837, AC004797, AC007114, AL049594, AC004159, AC005250, AC005057, AL035587, AL033521, AC004883, AL031295, AC006222, AC004987, AC005488, AC002416, AC007406, AP000030, AL035458, AC007172, AL031984, AL137294, Z82206, AP000514, AC005048, AC006039, AC009286,				
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					AC006112, AF091512, and AP000344.
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**TABLE 4**

<b>Code</b>	<b>Description</b>	<b>Tissue</b>	<b>Organ</b>	<b>Cell Line</b>	<b>Disease</b>	<b>Vector</b>
AR022	a_Heart	a_Heart				
AR023	a_Liver	a_Liver				
AR024	a_mammary gland	a_mammary gland				
AR025	a_Prostate	a_Prostate				
AR026	a_small intestine	a_small intestine				
AR027	a_Stomach	a_Stomach				
AR028	Blood B cells	Blood B cells				
AR029	Blood B cells activated	Blood B cells activated				
AR030	Blood B cells resting	Blood B cells resting				
AR031	Blood T cells activated	Blood T cells activated				
AR032	Blood T cells resting	Blood T cells resting				
AR033	brain	brain				
AR034	breast	breast				
AR035	breast cancer	breast cancer				
AR036	Cell Line CAOV3	Cell Line CAOV3				
AR037	cell line PA-1	cell line PA-1				
AR038	cell line transformed	cell line transformed				
AR039	colon	colon				
AR040	colon (9808co65R)	colon (9808co65R)				
AR041	colon (9809co15)	colon (9809co15)				
AR042	colon cancer	colon cancer				
AR043	colon cancer (9808co64R)	colon cancer (9808co64R)				
AR044	colon cancer 9809co14	colon cancer 9809co14				
AR045	corn clone 5	corn clone 5				
AR046	corn clone 6	corn clone 6				
AR047	corn clone2	corn clone2				
AR048	corn clone3	corn clone3				
AR049	Corn Clone4	Corn Clone4				
AR050	Donor II B Cells 24hrs	Donor II B Cells 24hrs				
AR051	Donor II B Cells 72hrs	Donor II B Cells 72hrs				
AR052	Donor II B-Cells 24 hrs.	Donor II B-Cells 24 hrs.				
AR053	Donor II B-Cells 72hrs	Donor II B-Cells 72hrs				
AR054	Donor II Resting B Cells	Donor II Resting B Cells				
AR055	Heart	Heart				
AR056	Human Lung (clonotech)	Human Lung (clonotech)				
AR057	Human Mammary (clontech)	Human Mammary (clontech)				
AR058	Human Thymus (clonotech)	Human Thymus (clonotech)				
AR059	Jurkat (unstimulated)	Jurkat (unstimulated)				
AR060	Kidney	Kidney				
AR061	Liver	Liver				
AR062	Liver (Clontech)	Liver (Clontech)				
AR063	Lymphocytes chronic	Lymphocytes				

	lymphocytic leukaemia	chronic lymphocytic leukaemia				
AR064	Lymphocytes diffuse large B cell lymphoma	Lymphocytes diffuse large B cell lymphoma				
AR065	Lymphocytes follicular lymphoma	Lymphocytes follicular lymphoma				
AR066	normal breast	normal breast				
AR067	Normal Ovarian (4004901)	Normal Ovarian (4004901)				
AR068	Normal Ovary 9508G045	Normal Ovary 9508G045				
AR069	Normal Ovary 9701G208	Normal Ovary 9701G208				
AR070	Normal Ovary 9806G005	Normal Ovary 9806G005				
AR071	Ovarian Cancer	Ovarian Cancer				
AR072	Ovarian Cancer (9702G001)	Ovarian Cancer (9702G001)				
AR073	Ovarian Cancer (9707G029)	Ovarian Cancer (9707G029)				
AR074	Ovarian Cancer (9804G011)	Ovarian Cancer (9804G011)				
AR075	Ovarian Cancer (9806G019)	Ovarian Cancer (9806G019)				
AR076	Ovarian Cancer (9807G017)	Ovarian Cancer (9807G017)				
AR077	Ovarian Cancer (9809G001)	Ovarian Cancer (9809G001)				
AR078	ovarian cancer 15799	ovarian cancer 15799				
AR079	Ovarian Cancer 17717AID	Ovarian Cancer 17717AID				
AR080	Ovarian Cancer 4004664B1	Ovarian Cancer 4004664B1				
AR081	Ovarian Cancer 4005315A1	Ovarian Cancer 4005315A1				
AR082	ovarian cancer 94127303	ovarian cancer 94127303				
AR083	Ovarian Cancer 96069304	Ovarian Cancer 96069304				
AR084	Ovarian Cancer 9707G029	Ovarian Cancer 9707G029				
AR085	Ovarian Cancer 9807G045	Ovarian Cancer 9807G045				
AR086	ovarian cancer 9809G001	ovarian cancer 9809G001				
AR087	Ovarian Cancer 9905C032RC	Ovarian Cancer 9905C032RC				
AR088	Ovarian cancer 9907 C00 3rd	Ovarian cancer 9907 C00 3rd				
AR089	Prostate	Prostate				
AR090	Prostate (clonotech)	Prostate (clonotech)				
AR091	prostate cancer	prostate cancer				
AR092	prostate cancer #15176	prostate cancer #15176				
AR093	prostate cancer #15509	prostate cancer #15509				
AR094	prostate cancer #15673	prostate cancer #15673				
AR095	Small Intestine	Small Intestine				

	(Clontech)	(Clontech)				
AR096	Spleen	Spleen				
AR097	Thymus T cells activated	Thymus T cells activated				
AR098	Thymus T cells resting	Thymus T cells resting				
AR099	Tonsil	Tonsil				
AR100	Tonsil germinal center centroblast	Tonsil germinal center centroblast				
AR101	Tonsil germinal center B cell	Tonsil germinal center B cell				
AR102	Tonsil lymph node	Tonsil lymph node				
AR103	Tonsil memory B cell	Tonsil memory B cell				
AR104	Whole Brain	Whole Brain				
AR105	Xenograft ES-2	Xenograft ES-2				
AR106	Xenograft SW626	Xenograft SW626				
H0041	Human Fetal Bone	Human Fetal Bone	Bone			Uni-ZAP XR
H0122	Human Adult Skeletal Muscle	Human Skeletal Muscle	Sk Muscle			Uni-ZAP XR
H0124	Human Rhabdomyosarcoma	Human Rhabdomyosarcoma	Sk Muscle		disease	Uni-ZAP XR
H0135	Human Synovial Sarcoma	Human Synovial Sarcoma	Synovium			Uni-ZAP XR
H0251	Human Chondrosarcoma	Human Chondrosarcoma	Cartilage		disease	Uni-ZAP XR
H0252	Human Osteosarcoma	Human Osteosarcoma	Bone		disease	Uni-ZAP XR
H0381	Bone Cancer	Bone Cancer			disease	Uni-ZAP XR
H0419	Bone Cancer, re-excision	Bone Cancer				Uni-ZAP XR
H0529	Myeloid Progenitor Cell Line	TF-1 Cell Line; Myeloid progenitor cell line				pCMVSPORT 3.0
H0636	Chondrocytes	Chondrocytes				pSport1
H0658	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	9809C332- Poorly differentiate	Ovary & Fallopian Tubes		disease	pSport1
S0001	Brain frontal cortex	Brain frontal cortex	Brain			Lambda ZAP II
S0003	Human Osteoclastoma	Osteoclastoma	bone		disease	Uni-ZAP XR
S0011	STROMAL - OSTEOCLASTOMA	Osteoclastoma	bone		disease	Uni-ZAP XR
S0022	Human Osteoclastoma Stromal Cells - unamplified	Osteoclastoma Stromal Cells				Uni-ZAP XR
S0027	Smooth muscle, serum treated	Smooth muscle	Pulmonary artery	Cell Line		Uni-ZAP XR
S0028	Smooth muscle, control	Smooth muscle	Pulmonary artery	Cell Line		Uni-ZAP XR
S0032	Smooth muscle-IL1b induced	Smooth muscle	Pulmonary artery	Cell Line		Uni-ZAP XR
S0037	Smooth muscle, IL1b induced	Smooth muscle	Pulmonary artery	Cell Line		Uni-ZAP XR
S0118	Smooth muscle control 2	Smooth muscle	Pulmonary artery	Cell Line		Uni-ZAP XR
S0122	Osteoclastoma-	Osteoclastoma	bone		disease	pBluescript

	normalized A					
S0126	Osteoblasts	Osteoblasts	Knee	Cell Line		Uni-ZAP XR
S0192	Synovial Fibroblasts (control)	Synovial Fibroblasts				pSport1
S0194	Synovial hypoxia	Synovial Fibroblasts				pSport1
S0196	Synovial IL-1/TNF stimulated	Synovial Fibroblasts				pSport1
S0206	Smooth Muscle-HASTE normalized	Smooth muscle	Pulmonary artery	Cell Line		pBluescript
S0214	Human Osteoclastoma, re-excision	Osteoclastoma	bone		disease	Uni-ZAP XR
S0242	Synovial Fibroblasts (IL1/TNF), sub	Synovial Fibroblasts				pSport1
S0250	Human Osteoblasts II	Human Osteoblasts	Femur		disease	pCMVSPORT 2.0
S0276	Synovial hypoxia-RSF subtracted	Synovial fibroblasts (rheumatoid)	Synovial tissue			pSport1
S0312	Human osteoarthritic;fraction II	Human osteoarthritic cartilage			disease	pSport1
S0314	Human osteoarthritis;fraction I	Human osteoarthritic cartilage			disease	pSport1
S0316	Human Normal Cartilage,Fraction I	Human Normal Cartilage				pSport1
S0318	Human Normal Cartilage Fraction II	Human Normal Cartilage				pSport1
S0334	Human Normal Cartilage Fraction III	Human Normal Cartilage				pSport1
S0336	Human Normal Cartilage Fraction IV	Human Normal Cartilage				pSport1
S0338	Human Osteoarthritic Cartilage Fraction III	Human osteoarthritic cartilage			disease	pSport1
S0340	Human Osteoarthritic Cartilage Fraction IV	Human osteoarthritic cartilage			disease	pSport1
S0362	Human Gastrocnemius	Gastrocnemius muscle				pSport1
S0390	Smooth muscle, control; re-excision	Smooth muscle	Pulmonary artery	Cell Line		Uni-ZAP XR
S3012	Smooth Muscle Serum Treated, Norm	Smooth muscle	Pulmonary artery	Cell Line		pBluescript
S3014	Smooth muscle, serum induced,re-exc	Smooth muscle	Pulmonary artery	Cell Line		pBluescript
L0021	Human adult (K.Okubo)					
L0022	Human adult lung 3" directed MboI cDNA					
L0040	Human colon mucosa					
L0055	Human promyelocyte					
L0180	Human GM-CSF-deprived TF-1 cell line (Liu,Hongtao)			GM-CSF-deprived TF-1 cell line		
L0361	Stratagene ovary (#937217)		ovary			Bluescript SK
L0362	Stratagene ovarian cancer (#937219)					Bluescript SK-
L0365	NCI_CGAP_Phe1	pheochromocytoma				Bluescript

						SK-
L0366	Stratagene schizo brain S11	schizophrenic brain S-11 frontal lobe				Bluescript SK-
L0369	NCI_CGAP_AA1	adrenal adenoma	adrenal gland			Bluescript SK-
L0370	Johnston frontal cortex	pooled frontal lobe	brain			Bluescript SK-
L0375	NCI_CGAP_Kid6	kidney tumor	kidney			Bluescript SK-
L0384	NCI_CGAP_Pr23	prostate tumor	prostate			Bluescript SK-
L0387	NCI_CGAP_GCB0	germinal center B-cells	tonsil			Bluescript SK-
L0415	b4HB3MA Cot8-HAP-Ft					Lafmid BA
L0435	Infant brain, LLNL array of Dr. M. Soares 1NIB					lafmid BA
L0438	normalized infant brain cDNA	total brain	brain			lafmid BA
L0439	Soares infant brain 1NIB		whole brain			Lafmid BA
L0455	Human retina cDNA randomly primed sublibrary	retina	eye			lambda gt10
L0465	TEST1, Human adult Testis tissue					lambda nm1149
L0471	Human fetal heart, Lambda ZAP Express					Lambda ZAP Express
L0485	STRATAGENE Human skeletal muscle cDNA library, cat. #936215.	skeletal muscle	leg muscle			Lambda ZAPII
L0498	NCI_CGAP_HSC3	CD34+, T negative, patient with chronic myelogenous	bone marrow			pAMP1
L0517	NCI_CGAP_Pr1					pAMP10
L0518	NCI_CGAP_Pr2					pAMP10
L0520	NCI_CGAP_Alv1	alveolar rhabdomyosarcoma				pAMP10
L0521	NCI_CGAP_Ew1	Ewing's sarcoma				pAMP10
L0523	NCI_CGAP_Lip2	liposarcoma				pAMP10
L0526	NCI_CGAP_Pr12	metastatic prostate bone lesion				pAMP10
L0527	NCI_CGAP_Ov2	ovary				pAMP10
L0529	NCI_CGAP_Pr6	prostate				pAMP10
L0530	NCI_CGAP_Pr8	prostate				pAMP10
L0538	NCI_CGAP_Ov5	normal surface epithelium	ovary			pAMP10
L0545	NCI_CGAP_Pr4.1	prostatic intraepithelial neoplasia - high grade	prostate			pAMP10
L0559	NCI_CGAP_Ov39	papillary serous ovarian metastasis	ovary			pAMP10
L0562	Chromosome 7 HeLa cDNA Library			HeLa cell line; ATCC		pAMP10
L0581	Stratagene liver (#937224)		liver			pBluescript SK



L0586	HTCDL1					pBluescript SK(-)
L0588	Stratagene endothelial cell 937223					pBluescript SK-
L0589	Stratagene fetal retina 937202					pBluescript SK-
L0590	Stratagene fibroblast (#937212)					pBluescript SK-
L0591	Stratagene HeLa cell s3 937216					pBluescript SK-
L0592	Stratagene hNT neuron (#937233)					pBluescript SK-
L0594	Stratagene neuroepithelium NT2RAMI 937234					pBluescript SK-
L0595	Stratagene NT2 neuronal precursor 937230	neuroepithelial cells	brain			pBluescript SK-
L0596	Stratagene colon (#937204)		colon			pBluescript SK-
L0597	Stratagene corneal stroma (#937222)		cornea			pBluescript SK-
L0598	Morton Fetal Cochlea	cochlea	ear			pBluescript SK-
L0599	Stratagene lung (#937210)		lung			pBluescript SK-
L0601	Stratagene pancreas (#937208)		pancreas			pBluescript SK-
L0602	Pancreatic Islet	pancreatic islet	pancreas			pBluescript SK-
L0604	Stratagene muscle 937209	muscle	skeletal muscle			pBluescript SK-
L0605	Stratagene fetal spleen (#937205)	fetal spleen	spleen			pBluescript SK-
L0606	NCL_CGAP_Lym5	follicular lymphoma	lymph node			pBluescript SK-
L0607	NCL_CGAP_Lym6	mantle cell lymphoma	lymph node			pBluescript SK-
L0608	Stratagene lung carcinoma 937218	lung carcinoma	lung	NCI-H69		pBluescript SK-
L0623	HM3	pectoral muscle (after mastectomy)				pcDNAII (Invitrogen)
L0636	NCL_CGAP_Pit1	four pooled pituitary adenomas	brain			pCMV-SPORT6
L0640	NCL_CGAP_Br18	four pooled high-grade tumors, including two prima	breast			pCMV-SPORT6
L0646	NCL_CGAP_Co14	moderately-differentiated adenocarcinoma	colon			pCMV-SPORT6
L0653	NCL_CGAP_Lu28	two pooled squamous cell carcinomas	lung			pCMV-SPORT6
L0655	NCL_CGAP_Lym12	lymphoma, follicular mixed small and large cell	lymph node			pCMV-SPORT6
L0659	NCL_CGAP_Pan1	adenocarcinoma	pancreas			pCMV-SPORT6
L0661	NCL_CGAP_Mel15	malignant melanoma, metastatic to lymph	skin			pCMV-SPORT6

		node				
L0662	NCI_CGAP_Gas4	poorly differentiated adenocarcinoma with signet r	stomach			pCMV-SPORT6
L0663	NCI_CGAP_Ut2	moderately-differentiated endometrial adenocarcino	uterus			pCMV-SPORT6
L0665	NCI_CGAP_Ut4	serous papillary carcinoma, high grade, 2 pooled t	uterus			pCMV-SPORT6
L0666	NCI_CGAP_Ut1	well-differentiated endometrial adenocarcinoma, 7	uterus			pCMV-SPORT6
L0731	Soares_pregnant_uterus_NbHPU		uterus			pT7T3-Pac
L0740	Soares melanocyte 2NbHM	melanocyte				pT7T3D (Pharmacia) with a modified polylinker
L0741	Soares adult brain N2b4HB55Y		brain			pT7T3D (Pharmacia) with a modified polylinker
L0742	Soares adult brain N2b5HB55Y		brain			pT7T3D (Pharmacia) with a modified polylinker
L0743	Soares breast 2NbHBst		breast			pT7T3D (Pharmacia) with a modified polylinker
L0744	Soares breast 3NbHBst		breast			pT7T3D (Pharmacia) with a modified polylinker
L0745	Soares retina N2b4HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0746	Soares retina N2b5HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0747	Soares_fetal_heart_NbH H19W		heart			pT7T3D (Pharmacia) with a modified polylinker
L0748	Soares fetal liver spleen 1NFLS		Liver and Spleen			pT7T3D (Pharmacia) with a modified polylinker
L0749	Soares_fetal_liver_splee		Liver and			pT7T3D

	n_1NFLS_S1		Spleen			(Pharmacia) with a modified polylinker
L0750	Soares_fetal_lung_NbH L19W		lung			pT7T3D (Pharmacia) with a modified polylinker
L0751	Soares ovary tumor NbHOT	ovarian tumor	ovary			pT7T3D (Pharmacia) with a modified polylinker
L0752	Soares_parathyroid_tum or_NbHPA	parathyroid tumor	parathyroi d gland			pT7T3D (Pharmacia) with a modified polylinker
L0753	Soares_pineal_gland_N 3HPG		pineal gland			pT7T3D (Pharmacia) with a modified polylinker
L0754	Soares placenta Nb2HP		placenta			pT7T3D (Pharmacia) with a modified polylinker
L0755	Soares_placenta_8to9we eks_2NbHP8to9W		placenta			pT7T3D (Pharmacia) with a modified polylinker
L0756	Soares_multiple_scleros is_2NbHMSP	multiple sclerosis lesions				pT7T3D (Pharmacia) with a modified polylinker V_TYPE
L0757	Soares_senescent_fibrobl asts_NbHSF	senescent fibroblast				pT7T3D (Pharmacia) with a modified polylinker V_TYPE
L0758	Soares_testis_NHT					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0759	Soares_total_fetus_Nb2 HF8_9w					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0760	Barstead aorta HPLRB3	aorta				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0761	NCI_CGAP_CLL1	B-cell, chronic				pT7T3D-Pac

		lymphotic leukemia				(Pharmacia) with a modified polylinker
L0763	NCI_CGAP_Br2	breast				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0764	NCI_CGAP_Co3	colon				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0766	NCI_CGAP_GCB1	germinal center B cell				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0768	NCI_CGAP_GC4	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0769	NCI_CGAP_Brn25	anaplastic oligodendroglioma	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0770	NCI_CGAP_Brn23	glioblastoma (pooled)	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0774	NCI_CGAP_Kid3		kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0775	NCI_CGAP_Kid5	2 pooled tumors (clear cell type)	kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0776	NCI_CGAP_Lu5	carcinoid	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0777	Soares_NhHMPu_S1	Pooled human melanocyte, fetal heart, and pregnant	mixed (see below)			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0779	Soares_NFL_T_GBC_S 1		pooled			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0780	Soares_NSF_F8_9W_O T_PA_P_S1		pooled			pT7T3D-Pac (Pharmacia) with a

						modified polylinker
L0783	NCI_CGAP_Pr22	normal prostate	prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0787	NCI_CGAP_Sub1					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0788	NCI_CGAP_Sub2					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0789	NCI_CGAP_Sub3					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0790	NCI_CGAP_Sub4					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0792	NCI_CGAP_Sub6					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0794	NCI_CGAP_GC6	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0796	NCI_CGAP_Brn50	medulloblastoma	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0800	NCI_CGAP_Co16	colon tumor, RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0803	NCI_CGAP_Kid11		kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0804	NCI_CGAP_Kid12	2 pooled tumors (clear cell type)	kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0805	NCI_CGAP_Lu24	carcinoid	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker

L0806	NCI_CGAP_Lu19	squamous cell carcinoma, poorly differentiated (4	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0807	NCI_CGAP_Ov18	fibrotheoma	ovary			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0809	NCI_CGAP_Pr28		prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L2245	NEM subtracted human fetal kidney cDNA					pUEX1
L2251	Human fetal lung	Fetal lung				

**TABLE 5**

<b>OMIM Reference</b>	<b>Description</b>
104770	Amyloidosis, secondary, susceptibility to
107670	Apolipoprotein A-II deficiency
109270	Renal tubular acidosis, distal, 179800
109270	Spherocytosis, hereditary
109270	[Acanthocytosis, one form]
109270	[Elliptocytosis, Malaysian-Melanesian type]
109270	Hemolytic anemia due to band 3 defect
110700	Vivax malaria, susceptibility to
114208	Malignant hyperthermia susceptibility 5, 601887
114208	Hypokalemic periodic paralysis, 170400
114290	Campomelic dysplasia with autosomal sex reversal
118210	Charcot-Marie-Tooth neuropathy-2A
119300	van der Woude syndrome
120110	Metaphyseal chondrodysplasia, Schmid type
120150	Osteogenesis imperfecta, 4 clinical forms, 166200, 166210, 259420, 166220
120150	Osteoporosis, idiopathic, 166710
120150	Ehlers-Danlos syndrome, type VIIA1, 130060
120160	Osteogenesis imperfecta, 4 clinical forms, 166200, 166210, 259420, 166220
120160	Osteoporosis, idiopathic, 166710
120160	Ehlers-Danlos syndrome, type VIIA2, 130060
120160	Marfan syndrome, atypical
120550	C1q deficiency, type A
120570	C1q deficiency, type B
120575	C1q deficiency, type C

120620	SLE susceptibility
120620	CR1 deficiency
120920	Measles, susceptibility to
121014	Heterotaxia, viscerotaxial, autosomal recessive
121800	Corneal dystrophy, crystalline, Schnyder
123829	Melanoma
126650	Chloride diarrhea, congenital, Finnish type, 214700
126650	Colon cancer
130500	Elliptocytosis-1
133200	Erythrokeratoderma variabilis
133701	Exostoses, multiple, type 2
134370	Factor H deficiency
134370	Hemolytic-uremic syndrome, 235400
134370	Membroproliferative glomerulonephritis
134580	Factor XIII B deficiency
136550	Macular dystrophy, North Carolina type
138033	Diabetes mellitus, type II
138140	Glucose transport defect, blood-brain barrier
138971	Kostmann neutropenia, 202700
139250	Isolated growth hormone deficiency, Illig type with absent GH and Kowarski type with bioinactive GH
144200	Epidermolytic palmoplantar keratoderma
145001	Hyperparathyroidism-jaw tumor syndrome
145260	Pseudohypoadosteronism, type II
146760	[IgG receptor I, phagocytic, familial deficiency of]
146790	Lupus nephritis, susceptibility to
147570	Interferon, immune, deficiency
148065	White sponge nevus, 193900
148066	Epidermolysis bullosa simplex, Koebner, Dowling-Meara, and Weber-Cockayne types, 131900, 131760, 131800
148066	Epidermolysis bullosa simplex, recessive, 601001
148067	Nonepidermolytic palmoplantar keratoderma, 600962
148067	Pachyonychia congenita, Jadassohn-Lewandowsky type, 167200
148069	Pachyonychia congenita, Jackson-Lawler type, 167210
148080	Epidermolytic hyperkeratosis, 113800
150200	[Placental lactogen deficiency]
150240	Cutis laxa, marfanoid neonatal type
150292	Epidermolysis bullosa, Herlitz junctional type, 226700
150310	Epidermolysis bullosa, Herlitz junctional type, 226700
150310	Epidermolysis bullosa, generalized atrophic benign, 226650
152760	Hypogonadotropic hypogonadism due to GNRH deficiency, 227200
153454	Ehlers-Danlos syndrome, type VI, 225400
154275	Malignant hyperthermia susceptibility 2
154276	Malignant hyperthermia susceptibility 3

156490	Neuroblastoma
159001	Muscular dystrophy, limb-girdle, type 1B
162100	Neuralgic amyotrophy with predilection for brachial plexus
164731	Ovarian carcinoma, 167000
168500	Parietal foramina
170500	Myotonia congenita, atypical acetazolamide-responsive
170500	Paramyotonia congenita, 168300
170500	Hyperkalemic periodic paralysis
170995	Zellweger syndrome-2
171190	Hypertension, essential, 145500
171650	Lysosomal acid phosphatase deficiency
171760	Hypophosphatasia, adult, 146300
171760	Hypophosphatasia, infantile, 241500
172400	Hemolytic anemia due to glucosephosphate isomerase deficiency
172400	Hydrops fetalis, one form
172411	Colorectal cancer, resistance to
173360	Thrombophilia due to excessive plasminogen activator inhibitor
173360	Hemorrhagic diathesis due to PAI1 deficiency
173370	Plasminogen activator deficiency
175100	Turcot syndrome, 276300
175100	Adenomatous polyposis coli
175100	Adenomatous polyposis coli, attenuated
175100	Colorectal cancer
175100	Desmoid disease, hereditary, 135290
175100	Gardner syndrome
176930	Dysprothrombinemia
176930	Hypoprothrombinemia
176960	Pituitary tumor, invasive
179820	[Hyperproreninemia]
180100	Retinitis pigmentosa-1
180105	Retinitis pigmentosa-10
180240	Leukemia, acute promyelocytic
180860	Russell-Silver syndrome
180901	Malignant hyperthermia susceptibility 1, 145600
180901	Central core disease, 117000
181430	Scapuloperoneal syndrome, myopathic type
182138	Anxiety-related personality traits
185430	Atherosclerosis, susceptibility to
185470	Myopathy due to succinate dehydrogenase deficiency
185800	Symphalangism, proximal
190900	Colorblindness, tritan
191045	Cardiomyopathy, familial hypertrophic, 2, 115195
191315	Insensitivity to pain, congenital, with anhidrosis, 256800
191540	[Urate oxidase deficiency]
203310	Ocular albinism, autosomal recessive



208250	Jacobs syndrome
217300	Cornea plana congenita, recessive
221770	Polycystic lipomembranous osteodysplasia with sclerosing leukencephalopathy
221820	Gliososis, familial progressive subcortical
222800	Hemolytic anemia due to bisphosphoglycerate mutase deficiency
226450	Epidermolysis bullosa inversa, junctional
230350	Galactose epimerase deficiency
236250	Homocystinuria due to MTHFR deficiency
246900	Lipoamide dehydrogenase deficiency
248600	Maple syrup urine disease, type Ia
249000	Meckel syndrome
252940	Sanfilippo syndrome, type D
253200	Maroteaux-Lamy syndrome, several forms
253250	Mulibrey nanism
255800	Schwartz-Jampel syndrome
256700	Neuroblastoma
264470	Adrenoleukodystrophy, pseudoneonatal
264700	Pseudo-vitamin D dependency rickets 1
270800	Spastic paraplegia-5A
274270	Thymine-uraciluria
274270	Fluorouracil toxicity, sensitivity to
277700	Werner syndrome
300031	Mental retardation, X-linked, FRAXF type
300044	Wernicke-Korsakoff syndrome, susceptibility to
300048	Intestinal pseudoobstruction, neuronal, X-linked
300049	Nodular heterotopia, bilateral periventricular
300049	BPNH/MR syndrome
300055	Mental retardation with psychosis, pyramidal signs, and macroorchidism
300100	Adrenoleukodystrophy
300100	Adrenomyeloneuropathy
300104	Mental retardation, X-linked nonspecific, 309541
300126	Dyskeratosis congenita-1, 305000
301201	Amelogenesis imperfecta-3, hypoplastic type
301590	Anophthalmos-1
302060	Noncompaction of left ventricular myocardium, isolated
302060	Barth syndrome
302060	Cardiomyopathy, X-linked dilated, 300069
302060	Endocardial fibroelastosis-2
302960	Chondrodysplasia punctata, X-linked dominant
303700	Colorblindness, blue monochromatic
303800	Colorblindness, deutan
303900	Colorblindness, protan
304800	Diabetes insipidus, nephrogenic

305900	Favism
305900	G6PD deficiency
305900	Hemolytic anemia due to G6PD deficiency
306700	Hemophilia A
306995	[Homosexuality, male]
308310	Incontinentia pigmenti, familial
308840	Spastic paraplegia, 312900
308840	Hydrocephalus due to aqueductal stenosis, 307000
308840	MASA syndrome, 303350
309200	Manic-depressive illness, X-linked
309548	Mental retardation, X-linked, FRAXE type
309620	Mental retardation-skeletal dysplasia
309900	Mucopolysaccharidosis II
310300	Emery-Dreifuss muscular dystrophy
310400	Myotubular myopathy, X-linked
310460	Myopia-1
310460	Bornholm eye disease
311300	Otopalatodigital syndrome, type I
311510	Waisman parkinsonism-mental retardation syndrome
314300	Goeminne TKCR syndrome
314400	Cardiac valvular dysplasia-1
600105	Retinitis pigmentosa-12, autosomal recessive
600119	Muscular dystrophy, Duchenne-like, type 2
600119	Adhalinopathy, primary
600309	Atrioventricular canal defect-1
600525	Trichodontoosseous syndrome, 190320
600623	Prostate cancer, 176807
600759	Alzheimer disease-4
600808	Enuresis, nocturnal, 2
600811	Xeroderma pigmentosum, group E, DDB-negative subtype, 278740
600852	Retinitis pigmentosa-17
600881	Cataract, congenital, zonular, with sutural opacities
600887	Endometrial carcinoma
600897	Cataract, zonular pulverulent-1, 116200
600918	Cystinuria, type III
600958	Cardiomyopathy, familial hypertrophic, 4, 115197
600995	Nephrotic syndrome, idiopathic, steroid-resistant
601284	Hereditary hemorrhagic telangiectasia-2, 600376
601363	Wilms tumor, type 4
601412	Deafness, autosomal dominant 7
601414	Retinitis pigmentosa-18
601494	Cardiomyopathy, familial, dilated-2
601652	Glaucoma 1A, primary open angle, juvenile-onset, 137750
601666	Insulin-dependent diabetes mellitus-15

601687	Meesmann corneal dystrophy, 122100
601769	Osteoporosis, involutional
601769	Rickets, vitamin D-resistant, 277440
601844	Pseudohypoaldosteronism type II
601863	Bare lymphocyte syndrome, complementation group C
601954	Muscular dystrophy, limb-girdle, type 2G
601975	Ectodermal dysplasia/skin fragility syndrome
602094	Lipodystrophy, familial partial
602116	Glioma
602136	Refsum disease, infantile, 266510
602136	Zellweger syndrome-1, 214100
602136	Adrenoleukodystrophy, neonatal, 202370
602447	Coronary artery disease, susceptibility to
602491	Hyperlipidemia, familial combined, 1
602629	Dystonia-6, torsion
602716	Nephrosis-1, congenital, Finnish type, 256300
602771	Muscular dystrophy, congenital, with early spine rigidity
602772	Retinitis pigmentosa-24

#### *Polynucleotide and Polypeptide Variants*

[0105] The present invention is also directed to variants of the musculoskeletal system associated polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, nucleotide sequences encoding the polypeptide of SEQ ID NO:Y, the nucleotide sequence of SEQ ID NO:X encoding the polypeptide sequence as defined in column 6 of Table 1A, nucleotide sequences encoding the polypeptide as defined in column 6 of Table 1A, the nucleotide sequence as defined in columns 8 and 9 of Table 2, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, the nucleotide sequence as defined in column 6 of Table 1B, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in column 6 of Table 1B, the cDNA sequence contained in Clone ID NO:Z, and/or nucleotide sequences encoding a polypeptide encoded by the cDNA sequence contained in Clone ID NO:Z.

[0106] The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y, a polypeptide sequence as defined in column 6 of Table 1A, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the nucleotide sequence as defined in

columns 8 and 9 of Table 2, a polypeptide sequence encoded by the nucleotide sequence as defined in column 6 of Table 1B, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, and/or a polypeptide sequence encoded by the cDNA sequence contained in Clone ID NO:Z.

[0107] "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

[0108] Thus, one aspect of the invention provides an isolated nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide having a nucleotide sequence selected from the group consisting of: (a) a nucleotide sequence described in SEQ ID NO:X or contained in the cDNA sequence of Clone ID NO:Z; (b) a nucleotide sequence in SEQ ID NO:X or the cDNA in Clone ID NO:Z which encodes a mature musculoskeletal system associated polypeptide; (c) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of Clone ID NO:Z, which encodes a biologically active fragment of a musculoskeletal system associated polypeptide; (d) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of Clone ID NO:Z, which encodes an antigenic fragment of a musculoskeletal system associated polypeptide; (e) a nucleotide sequence encoding a musculoskeletal system associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (f) a nucleotide sequence encoding a mature musculoskeletal system associated polypeptide of the amino acid sequence of SEQ ID NO:Y or the amino acid sequence encoded by the cDNA in Clone ID NO:Z; (g) a nucleotide sequence encoding a biologically active fragment of a musculoskeletal system associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (h) a nucleotide sequence encoding an antigenic fragment of a musculoskeletal system associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; and (i) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), or (h), above.

[0109] The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the cDNA contained in Clone ID NO:Z or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in Clone ID NO:Z, the nucleotide coding sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, the nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto, the nucleotide sequence in SEQ ID NO:X encoding the polypeptide sequence as defined in column 6 of Table 1A or the complementary strand thereto, nucleotide sequences encoding a polypeptide as defined in column 6 of Table 1A or the complementary strand thereto, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides and nucleic acids.

[0110] In a preferred embodiment, the invention encompasses nucleic acid molecules which comprise, or alternatively, consist of a polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under lower stringency conditions, to a polynucleotide in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above, as are polypeptides encoded by these polynucleotides. In another preferred

embodiment, polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[0111] In another embodiment, the invention provides a purified protein comprising, or alternatively consisting of, a polypeptide having an amino acid sequence selected from the group consisting of: (a) the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (b) the amino acid sequence of a mature musculoskeletal system associated polypeptide having the amino acid sequence of SEQ ID NO:Y or the amino acid sequence encoded by the cDNA in Clone ID NO:Z; (c) the amino acid sequence of a biologically active fragment of a musculoskeletal system associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; and (d) the amino acid sequence of an antigenic fragment of a musculoskeletal system associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z.

[0112] The present invention is also directed to proteins which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the amino acid sequences in (a), (b), (c), or (d), above, the amino acid sequence shown in SEQ ID NO:Y, the amino acid sequence encoded by the cDNA contained in Clone ID NO:Z, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B, the amino acid sequence as defined in column 6 of Table 1A, an amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X, and an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X. Fragments of these polypeptides are also provided (e.g., those fragments described herein). Further proteins encoded by polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these amino acid sequences under stringent hybridization conditions or alternatively, under lower

stringency conditions, are also encompassed by the invention, as are the polynucleotides encoding these proteins.

[0113] By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence referred to in Table 1A or 2 as the ORF (open reading frame), or any fragment specified, as described herein.

[0114] As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

[0115] If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3'

truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

[0116] For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

[0117] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other



words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[0118] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of a polypeptide referred to in Table 1A (e.g., an amino acid sequence identified in columns 5 or 6) or Table 2 (e.g., the amino acid sequence of the polypeptide encoded by the polynucleotide sequence defined in columns 8 and 9 of Table 2) or a fragment thereof, the amino acid sequence of the polypeptide encoded by the polynucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B or a fragment thereof, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or an amino acid sequence of the polypeptide encoded by cDNA contained in Clone ID NO:Z, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237-245 (1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

[0119] If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N-

and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

[0120] For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

[0121] The polynucleotide variants of the invention may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide

variants containing alterations, which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, polypeptide variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

[0122] Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

[0123] Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptides of the present invention without substantial loss of biological function. As an example, the authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

[0124] Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem. 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the

molecule could be altered with little effect on either [binding or biological activity]." In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

[0125] Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0126] Thus, the invention further includes polypeptide variants which show a functional activity (e.g., biological activity) of the polypeptides of the invention. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

[0127] The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, (e.g., encoding a polypeptide having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having functional activity include, *inter alia*, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); (3) Northern Blot analysis for detecting mRNA expression in specific tissues (e.g., normal musculoskeletal system tissue or diseased

musculoskeletal system tissues); and (4) *in situ* hybridization (e.g., histochemistry) for detecting mRNA expression in specific tissues (e.g., normal musculoskeletal system tissue or diseased musculoskeletal system tissues).

[0128] Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having functional activity. By a polypeptide having "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide of the invention for binding) to an anti-polypeptide of the invention antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

[0129] The functional activity of the polypeptides, and fragments, variants and derivatives of the invention, can be assayed by various methods.

[0130] For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the present invention for binding to an anti-polypeptide of the invention antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, *in situ* immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

[0131] In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, the ability of physiological correlates of a polypeptide of the present invention to bind to a substrate(s) of the polypeptide of the invention can be routinely assayed using techniques known in the art.

[0132] In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants and derivatives thereof to elicit polypeptide related biological activity (either *in vitro* or *in vivo*). Other methods will be known to the skilled artisan and are within the scope of the invention.

[0133] Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA contained in Clone ID NO:Z, a nucleic acid sequence referred to in Table 1A (e.g., SEQ ID NO:X), a nucleic acid sequence disclosed in Table 2 (e.g., the nucleic acid sequence delineated in columns 8 and 9) or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

[0134] For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310

(1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

[0135] The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

[0136] The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. See Cunningham et al., Science 244:1081-1085 (1989). The resulting mutant molecules can then be tested for biological activity.

[0137] As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitutions, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitutions with one or more of the amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example,

polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, serum albumin (preferably human serum albumin) or a fragment or variant thereof, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

[0138] For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. See Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).

[0139] A further embodiment of the invention relates to polypeptides which comprise the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions from a polypeptide sequence disclosed herein. Of course it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, an amino acid sequence encoded by the complement of SEQ ID NO:X, and/or the amino acid sequence encoded by cDNA contained in Clone ID NO:Z which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions.

[0140] In specific embodiments, the polypeptides of the invention comprise, or alternatively, consist of, fragments or variants of a reference amino acid sequence selected from: (a) the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature form and/or other fragments described herein); (b) the amino acid sequence encoded by SEQ ID NO:X or fragments thereof; (c) the amino acid sequence encoded by the complement of SEQ ID NO:X or fragments thereof; (d) the amino acid



sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or fragments thereof; and (e) the amino acid sequence encoded by cDNA contained in Clone ID NO:Z or fragments thereof; wherein the fragments or variants have 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, amino acid residue additions, substitutions, and/or deletions when compared to the reference amino acid sequence. In preferred embodiments, the amino acid substitutions are conservative. Polynucleotides encoding these polypeptides are also encompassed by the invention.

#### *Polynucleotide and Polypeptide Fragments*

[0141] The present invention is also directed to polynucleotide fragments of the polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers to a polynucleotide having a nucleic acid sequence which, for example: is a portion of the cDNA contained in Clone ID NO:Z or the complementary strand thereto; is a portion of the polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in Clone ID NO:Z or the complementary strand thereto; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X; is a polynucleotide sequence encoding a portion of a polypeptide encoded by the complement of the polynucleotide sequence in SEQ ID NO:X; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto; or is a portion of the polynucleotide sequence of SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto.

[0142] The polynucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75

nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in Clone ID NO:Z, or the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 160, 170, 180, 190, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

[0143] Moreover, representative examples of polynucleotide fragments of the invention, comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of SEQ ID NO:X, or the complementary strand

thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[0144] Further representative examples of polynucleotide fragments of the invention, comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of the cDNA sequence contained in Clone ID NO:Z, or the complementary strand thereto. In this context "about" includes the

particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[0145] Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence delineated in Table 1B column 6. Additional, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence that is the complementary strand of a sequence delineated in column 6 of Table 1B. In further embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated Table 1B, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also

encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[0146] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1B, column 2) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0147] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0148] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in the same row of column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0149] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that

encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0150] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X (e.g., as described herein) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0151] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1B are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0152] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. In preferred

embodiments, the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B is directly contiguous with the 5' 10 polynucleotides of the next sequential exon delineated in Table 1B, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0153] In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y, a portion of an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, a portion of an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, and/or a portion of an amino acid sequence encoded by the cDNA contained in Clone ID NO:Z. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region. In a preferred embodiment, polypeptide fragments of the invention include, for example, fragments comprising, or alternatively consisting

of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

[0154] Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[0155] Accordingly, polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or



the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions is preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

[0156] The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X or the complement thereof, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1B, and/or a polypeptide encoded by the cDNA contained in Clone ID NO:Z). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y, or the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0157] The present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or a polypeptide encoded by the cDNA contained in Clone ID NO:Z). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where n corresponds to the position of amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0158] In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also

provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), the cDNA contained in Clone ID NO:Z, and/or the complement thereof, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0159] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[0160] The present application is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0161] Any polypeptide sequence encoded by, for example, the polynucleotide sequences set forth as SEQ ID NO:X or the complement thereof, (presented, for example, in Tables 1A and 2), the cDNA contained in Clone ID NO:Z, or the polynucleotide sequence as defined in column 6 of Table 1B, may be analyzed to

determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polynucleotide sequence of SEQ ID NO:X (e.g., the polypeptide of SEQ ID NO:Y and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2) or the cDNA contained in Clone ID NO:Z may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; <http://www.dnastar.com/>).

[0162] Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle hydrophilic regions and hydrophobic regions; Eisenberg alpha- and beta-amphipathic regions; Karplus-Schulz flexible regions; Emini surface-forming regions; and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

[0163] Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[0164] Preferred polypeptide fragments of the invention are fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a functional activity (e.g. biological activity) of the polypeptide sequence of which the amino acid sequence is a fragment. By a polypeptide displaying a "functional activity" is meant a polypeptide capable of one or more known functional activities associated with a full-

length protein, such as, for example, biological activity, antigenicity, immunogenicity, and/or multimerization, as described herein.

[0165] Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[0166] In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0167] The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of: the polypeptide sequence shown in SEQ ID NO:Y; a polypeptide sequence encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2; the polypeptide sequence encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1B or the complement thereto; the polypeptide sequence encoded by the cDNA contained in Clone ID NO:Z; or the polypeptide sequence encoded by a polynucleotide that hybridizes to the sequence of SEQ ID NO:X, the complement of the sequence of SEQ ID NO:X, the complement of a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, or the cDNA sequence contained in Clone ID NO:Z under stringent hybridization conditions or alternatively, under lower stringency hybridization as defined *supra*. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X, or a fragment thereof), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions defined *supra*.

[0168] The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and

most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross-reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

[0169] Fragments, which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

[0170] In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

[0171] Non-limiting examples of epitopes of polypeptides that can be used to generate antibodies of the invention include a polypeptide comprising, or alternatively consisting of, at least one, two, three, four, five, six or more of the portion(s) of SEQ

ID NO:Y specified in column 6 of Table 1A. These polypeptide fragments have been determined to bear antigenic epitopes of the proteins of the invention by the analysis of the Jameson-Wolf antigenic index, which is included in the DNASTar suite of computer programs. By "comprise" it is intended that a polypeptide contains at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y shown in column 6 of Table 1A, but it may contain additional flanking residues on either the amino or carboxyl termini of the recited portion. Such additional flanking sequences are preferably sequences naturally found adjacent to the portion; i.e., contiguous sequence shown in SEQ ID NO:Y. The flanking sequence may, however, be sequences from a heterologous polypeptide, such as from another protein described herein or from a heterologous polypeptide not described herein. In particular embodiments, epitope portions of a polypeptide of the invention comprise one, two, three, or more of the portions of SEQ ID NO:Y shown in column 6 of Table 1A. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0172] Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[0173] Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized

with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

[0174] As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention (e.g., those comprising an immunogenic or antigenic epitope) can be fused to heterologous polypeptide sequences. For example, polypeptides of the present invention (including fragments or variants thereof), may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof, resulting in chimeric polypeptides. By way of another non-limiting example, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred

embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide). Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

[0175] Such fusion proteins as those described above may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion desulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem*, 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin (HA) tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni<sup>2+</sup> nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.



***Fusion Proteins***

[0176] Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

[0177] Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

[0178] In certain preferred embodiments, proteins of the invention are fusion proteins comprising an amino acid sequence that is an N and/or C- terminal deletion of a polypeptide of the invention. In preferred embodiments, the invention is directed to a fusion protein comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence of the invention. Polynucleotides encoding these proteins are also encompassed by the invention.

[0179] Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

[0180] As one of skill in the art will appreciate that, as discussed above, polypeptides of the present invention, and epitope-bearing fragments thereof, can be combined with heterologous polypeptide sequences. For example, the polypeptides of the present invention may be fused with heterologous polypeptide sequences, for example, the polypeptides of the present invention may be fused with the constant

domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), or albumin (including, but not limited to, native or recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties (EP-A 0232 262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See, D. Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); K. Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995).

[0181] Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a polypeptide, which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., *Cell* 37:767 (1984).)

[0182] Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"), briefly described below, and further described herein. DNA shuffling may be employed to modulate the activities of

polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opin. Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference in its entirety). In a preferred embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc., of one or more heterologous molecules encoding a heterologous polypeptide.

[0183] Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

#### **Recombinant and Synthetic Production of Polypeptides of the Invention**

[0184] The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by synthetic and recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

[0185] The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells.

[0186] The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli lac*, *trp*, *phoA* and *tac* promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination,

and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

[0187] As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance, glutamine synthase, for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, 293, NSO and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

[0188] Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

[0189] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulfoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors is the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by

providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657, which are hereby incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors can be obtained from Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are herein incorporated by reference.

[0190] The present invention also relates to host cells containing the above-described vector constructs described herein, and additionally encompasses host cells containing nucleotide sequences of the invention that are operably associated with one or more heterologous control regions (e.g., promoter and/or enhancer) using techniques known of in the art. The host cell can be a higher eukaryotic cell, such as a mammalian cell (e.g., a human derived cell), or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. A host strain may be chosen, which modulates the expression of the inserted gene sequences, or modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically engineered polypeptide may be controlled. Furthermore, different host cells have characteristics and specific mechanisms for the translational and post-translational processing and modification (e.g., phosphorylation, cleavage) of proteins. Appropriate cell lines can be chosen to ensure the desired modifications and processing of the foreign protein expressed.

[0191] Introduction of the nucleic acids and nucleic acid constructs of the invention into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis *et al.*, *Basic Methods In Molecular Biology* (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

[0192] In addition to encompassing host cells containing the vector constructs

discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., musculoskeletal system antigen coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with musculoskeletal system associated polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous musculoskeletal system associated polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous musculoskeletal system associated polynucleotide sequences via homologous recombination (see, e.g., US Patent Number 5,641,670, issued June 24, 1997; International Publication Number WO 96/29411; International Publication Number WO 94/12650; Koller *et al.*, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); and Zijlstra *et al.*, *Nature* 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[0193] Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

[0194] In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a

methylophilic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolism pathway is the oxidation of methanol to formaldehyde using O<sub>2</sub>. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O<sub>2</sub>. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See, Ellis, S.B., *et al.*, *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., *et al.*, *Yeast* 5:167-77 (1989); Tschopp, J.F., *et al.*, *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

[0195] In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

[0196] Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

[0197] In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be

achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

[0198] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[0199] In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., Nature, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid,  $\alpha$ -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid



analogues in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0200] The invention encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease,  $\text{NaBH}_4$ ; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

[0201] Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

[0202] Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include iodine ( $^{121}\text{I}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{111}\text{In}$ ,  $^{112}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{115\text{m}}\text{In}$ ), technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ , and  $^{97}\text{Ru}$ .

[0203] In specific embodiments, a polypeptide of the present invention or fragment or variant thereof is attached to macrocyclic chelators that associate with

radiometal ions, including but not limited to,  $^{177}\text{Lu}$ ,  $^{90}\text{Y}$ ,  $^{166}\text{Ho}$ , and  $^{153}\text{Sm}$ , to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators is  $^{111}\text{In}$ . In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator is  $^{90}\text{Y}$ . In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In other specific embodiments, DOTA is attached to an antibody of the invention or fragment thereof via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90 (1998); Peterson et al., Bioconjug. Chem. 10(4):553-7 (1999); and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50 (1999); which are hereby incorporated by reference in their entirety.

[0204] As mentioned, the musculoskeletal system associated proteins of the invention may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given musculoskeletal system associated polypeptide. Musculoskeletal system associated polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic musculoskeletal system associated polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993);

POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., *Meth. Enzymol.* 182:626-646 (1990); Rattan et al., *Ann. N.Y. Acad. Sci.* 663:48-62 (1992)).

[0205] Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0206] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

[0207] As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo et al., *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev et al., *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti et al., *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by

reference.

[0208] The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, such as, for example, the method disclosed in EP 0 401 384 (coupling PEG to G-CSF), herein incorporated by reference; see also Malik et al., Exp. Hematol. 20:1028-1035 (1992), reporting pegylation of GM-CSF using tresyl chloride. For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0209] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

[0210] One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the

N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[0211] As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992); Francis et al., Intern. J. of Hematol. 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

[0212] One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ( $\text{ClSO}_2\text{CH}_2\text{CF}_3$ ). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

[0213] Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in

International Publication No. WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

[0214] The number of polyethylene glycol moieties attached to each protein of the invention (i.e., the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992).

[0215] The musculoskeletal system associated polypeptides of the invention can be recovered and purified from chemical synthesis and recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Well known techniques for refolding protein may be employed to regenerate active conformation when the polypeptide is denatured during isolation and/or purification.

[0216] Musculoskeletal system associated polynucleotides and polypeptides may be used in accordance with the present invention for a variety of applications, particularly those that make use of the chemical and biological properties of musculoskeletal system associated antigens. Among these are applications in the detection, prevention, diagnosis and/or treatment of diseases associated with musculoskeletal system, such as e.g., bone disorders (e.g., osteoporosis, osteomyelitis, Paget's disease, and sciolosis); joint disorders (e.g., osteoarthritis, rheumatoid arthritis, infectious arthritis, systemic lupus erythematosus, gout, and Reiter's syndrome); ligament, tendon, and bursa disorders (e.g., bursitis, tendinitis, and tenosynovitis); muscle disorders (e.g., muscular dystrophy, Pompe's disease, periodic paralysis,

polymyalgia rheumatica, polymyositis, and Steinert's disease), neoplasms and/or cancers of musculoskeletal tissues (e.g., osteochondroma, benign chondroma, chondroblastoma, osteoid osteoma, and giant cell tumor), and/or those disorders described under "Musculoskeletal System Disorders". Additional applications relate to diagnosis and to treatment of disorders of cells, tissues and organisms. These aspects of the invention are discussed further below.

[0217] In a preferred embodiment, polynucleotides expressed in a particular tissue type are used to detect, diagnose, treat, prevent and/or prognose disorders associated with the tissue type.

[0218] The polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

[0219] Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer refers to a multimer containing only polypeptides corresponding to a protein of the invention (e.g., the amino acid sequence of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X or the complement of SEQ ID NO:X, the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or an amino acid sequence encoded by cDNA contained in Clone ID NO:Z (including fragments, variants, splice variants, and fusion proteins, corresponding to these as described herein)). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing two polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing three polypeptides having identical and/or different

amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

[0220] As used herein, the term heteromer refers to a multimer containing two or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

[0221] Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked by, for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or encoded by the cDNA contained in Clone ID NO:Z). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., U.S. Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the



invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

[0222] Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

[0223] Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

[0224] In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention

containing Flag® polypeptide sequence. In a further embodiment, proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

[0225] The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

[0226] Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by

reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

### **Antibodies**

[0227] Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of the invention (e.g., a polypeptide or fragment or variant of the amino acid sequence of SEQ ID NO:Y or a polypeptide encoded by the cDNA contained in Clone ID NO:Z, and/or an epitope, of the present invention) as determined by immunoassays well known in the art for assaying specific antibody-antigen binding. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), intracellularly-made antibodies (i.e., intrabodies), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

[0228] Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')<sub>2</sub>, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable

region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described *infra* and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

[0229] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutti, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

[0230] Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention, which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues, or listed in the Tables and Figures. Preferred epitopes of the invention include those shown in column 6 of Table 1A, as well as polynucleotides that encode these epitopes. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

[0231] Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that

bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies, which bind polypeptides encoded by polynucleotides, which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M.

[0232] The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

[0233] Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies, which disrupt the receptor/ligand interactions with the polypeptides of the

invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies, which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described *supra*). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

[0234] The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies, which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., *Blood* 92(6):1981-1988 (1998); Chen et al., *Cancer Res.* 58(16):3668-3678 (1998); Harrop et al., *J. Immunol.* 161(4):1786-1794 (1998); Zhu et al., *Cancer Res.* 58(15):3209-3214 (1998); Yoon et al., *J. Immunol.* 160(7):3170-3179 (1998); Prat et al., *J. Cell. Sci.* 111(Pt2):237-247 (1998); Pitard et al., *J. Immunol. Methods* 205(2):177-190 (1997); Liautard et al., *Cytokine* 9(4):233-241 (1997); Carlson et al., *J. Biol. Chem.* 272(17):11295-11301 (1997); Taryman et al., *Neuron*

14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

[0235] Antibodies of the present invention may be used, for example, to purify, detect, and target the polypeptides of the present invention, including both *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies have utility in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); incorporated by reference herein in its entirety.

[0236] As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387; the disclosures of which are incorporated herein by reference in their entireties.

[0237] The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

[0238] The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

[0239] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

[0240] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art



for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[0241] Accordingly, the present invention provides methods of generating monoclonal antibodies, as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

[0242] Another well known method for producing both polyclonal and monoclonal human B cell lines is transformation using Epstein Barr Virus (EBV). Protocols for generating EBV-transformed B cell lines are commonly known in the art, such as, for example, the protocol outlined in Chapter 7.22 of Current Protocols in Immunology, Coligan et al., Eds., 1994, John Wiley & Sons, NY, which is hereby incorporated in its entirety by reference herein. The source of B cells for transformation is commonly human peripheral blood, but B cells for transformation may also be derived from other sources including, but not limited to, lymph nodes, tonsil, spleen, tumor tissue, and infected tissues. Tissues are generally made into single cell suspensions prior to EBV transformation. Additionally, steps may be taken to either physically remove or inactivate T cells (e.g., by treatment with cyclosporin A) in B cell-containing samples, because T cells from individuals seropositive for anti-EBV antibodies can suppress B cell immortalization by EBV.

[0243] In general, the sample containing human B cells is inoculated with EBV, and cultured for 3-4 weeks. A typical source of EBV is the culture supernatant of the B95-8 cell line (ATCC #VR-1492). Physical signs of EBV transformation can generally be seen towards the end of the 3-4 week culture period. By phase-contrast microscopy, transformed cells may appear large, clear, hairy and tend to aggregate in tight clusters of cells. Initially, EBV lines are generally polyclonal. However, over prolonged periods of cell cultures, EBV lines may become monoclonal or polyclonal as a result of the selective outgrowth of particular B cell clones. Alternatively, polyclonal EBV transformed lines may be subcloned (e.g., by limiting dilution culture)

or fused with a suitable fusion partner and plated at limiting dilution to obtain monoclonal B cell lines. Suitable fusion partners for EBV transformed cell lines include mouse myeloma cell lines (e.g., SP2/0, X63-Ag8.653), heteromyeloma cell lines (human x mouse; e.g., SPAM-8, SBC-H20, and CB-F7), and human cell lines (e.g., GM 1500, SKO-007, RPMI 8226, and KR-4). Thus, the present invention also provides a method of generating polyclonal or monoclonal human antibodies against polypeptides of the invention or fragments thereof, comprising EBV-transformation of human B cells.

[0244] Antibody fragments, which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')<sub>2</sub> fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). F(ab')<sub>2</sub> fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain. For example, the antibodies of the present invention can also be generated using various phage display methods known in the art and as discussed in detail in the Examples (e.g., Example 10). In phage display methods, functional antibody domains are displayed on the surface of phage particles, which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S.

Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0245] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')<sub>2</sub> fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

[0246] Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known

in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., *Nature* 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, *Molecular Immunology* 28(4/5):489-498 (1991); Studnicka et al., *Protein Engineering* 7(6):805-814 (1994); Roguska. et al., *PNAS* 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

[0247] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

[0248] Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring, which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all

or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; 5,939,598; 6,075,181 and 6,114,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0249] Completely human antibodies, which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., *Bio/technology* 12:899-903 (1988)).

[0250] Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, *FASEB J.* 7(5):437-444; (1989) and Nissinoff, J. *Immunol.* 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand/receptor. For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or

to bind its ligand(s)/receptor(s), and thereby block its biological activity. Alternatively, antibodies, which bind to and enhance polypeptide multimerization and/or binding, and/or receptor/ligand multimerization, binding and/or signaling can be used to generate anti-idiotypes that function as agonists of a polypeptide of the invention and/or its ligand/receptor. Such agonistic anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens as agonists of the polypeptides of the invention or its ligand(s)/receptor(s). For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby promote or enhance its biological activity.

[0251] Intrabodies of the invention can be produced using methods known in the art, such as those disclosed and reviewed in Chen et al., Hum. Gene Ther. 5:595-601 (1994); Marasco, W.A., Gene Ther. 4:11-15 (1997); Rondon and Marasco, Annu. Rev. Microbiol. 51:257-283 (1997); Proba et al., J. Mol. Biol. 275:245-253 (1998); Cohen et al., Oncogene 17:2445-2456 (1998); Ohage and Steipe, J. Mol. Biol. 291:1119-1128 (1999); Ohage et al., J. Mol. Biol. 291:1129-1134 (1999); Wirtz and Steipe, Protein Sci. 8:2245-2250 (1999); Zhu et al., J. Immunol. Methods 231:207-222 (1999); and references cited therein.

#### *Polynucleotides Encoding Antibodies*

[0252] The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined *supra*, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y, to a polypeptide encoded by a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or to a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

[0253] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in

Kutmeier et al., *BioTechniques* 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0254] Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A<sup>+</sup> RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[0255] Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, *Molecular Cloning, A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[0256] In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within

framework regions, e.g., into human framework regions to humanize a non-human antibody, as described *supra*. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed *supra*, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

[0257] In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described *supra*, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

[0258] Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in *E. coli* may also be used (Skerra et al., Science 242:1038- 1041 (1988)).



*Methods of Producing Antibodies*

[0259] The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques. Methods of producing antibodies include, but are not limited to, hybridoma technology, EBV transformation, and other methods discussed herein as well as through the use recombinant DNA technology, as discussed below.

[0260] Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

[0261] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells

containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0262] A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990)).

[0263] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., EMBO J. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0264] In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[0265] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals

include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., *Methods in Enzymol.* 153:51-544 (1987)).

[0266] In addition, a host cell strain may be chosen, which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells, which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

[0267] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines, which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may

advantageously be used to engineer cell lines, which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

[0268] A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgp<sup>r</sup>t- or ap<sup>r</sup>t- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 (Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); TIB TECH 11(5):155-215 (1993)); and hyg<sup>r</sup>, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

[0269] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the

amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

[0270] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulfoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the present invention are commercially available from suppliers, including, for example Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington et al., Bio/technology 10:169(1992) and in Biblia and Robinson Biotechnol. Prog. 11:1 (1995) which are incorporated in their entireties by reference herein.

[0271] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0272] Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example,

by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

[0273] The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either *in vitro* or *in vivo*, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in *in vitro* immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., *supra*, and PCT publication WO 93/21232; EP 439,095; Naramura et al., *Immunol. Lett.* 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., *PNAS* 89:1428-1432 (1992); Fell et al., *J. Immunol.* 146:2446-2452 (1991), which are incorporated by reference in their entireties.

[0274] The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through

disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337- 11341 (1992) (said references incorporated by reference in their entireties).

[0275] As discussed, *supra*, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the *in vivo* half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See EP 394,827; Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. See, for example, Fountoulakis et al., J. Biochem. 270:3958-3964 (1995). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. See, for example, EP A 232,262. Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995)).



[0276] Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

[0277] The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention.

[0278] Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, <sup>213</sup>Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine,

lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0279] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor,  $\alpha$ -interferon,  $\beta$ -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- $\alpha$ , TNF- $\beta$ , AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[0280] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[0281] Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example., Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom

et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

[0282] Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[0283] An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

#### *Immunophenotyping*

[0284] The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. Translation products of the genes of the present invention may be useful as cell specific markers, or more specifically as cellular markers that are differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison et al., Cell, 96:737-49 (1999)).

[0285] These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the

screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

*Assays For Antibody Binding*

[0286] The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays, which can be used, include but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[0287] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al., eds., (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.16.1.

[0288] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g.,  $^{32}\text{P}$  or  $^{125}\text{I}$ ) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al., eds., (1994), *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York, section 10.8.1.

[0289] ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al., eds., (1994), *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York, section 11.2.1.

[0290] The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) in the presence of increasing amounts of an unlabeled second antibody.

[0291] Antibodies of the invention may be characterized using immunocytochemistry methods on cells (e.g., mammalian cells, such as CHO cells) transfected with a vector enabling the expression of a musculoskeletal system antigen or with vector alone using techniques commonly known in the art. Antibodies that bind musculoskeletal system antigen transfected cells, but not vector-only transfected cells, are musculoskeletal system antigen specific.

#### *Therapeutic Uses*

[0292] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited

to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0293] In a specific and preferred embodiment, the present invention is directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the diseases, disorders, or conditions of the musculoskeletal system, including, but not limited to, bone disorders (e.g., osteoporosis, osteomyelitis, Paget's disease, and sciolosis); joint disorders (e.g., osteoarthritis, rheumatoid arthritis, infectious arthritis, systemic lupus erythematosus, gout, and Reiter's syndrome); ligament, tendon, and bursa disorders (e.g., bursitis, tendinitis, and tenosynovitis); muscle disorders (e.g., muscular dystrophy, Pompe's disease, periodic paralysis, polymyalgia rheumatica, polymyositis, and Steinert's disease), neoplasms and/or cancers of musculoskeletal tissues (e.g., osteochondroma, benign chondroma, chondroblastoma, osteoid osteoma, and giant cell tumor), and/or those disorders described under "Musculoskeletal System Disorders". Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (e.g., antibodies directed to the full length protein expressed on the cell surface of a mammalian cell; antibodies directed to an epitope of a musculoskeletal system associated polypeptide of the invention (such as, a linear epitope (shown in Table 1A, column 6) or a conformational epitope), including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions of the musculoskeletal system described herein. The treatment and/or prevention of diseases, disorders, or conditions of the musculoskeletal system associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention

may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0294] A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[0295] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells, which interact with the antibodies.

[0296] The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

[0297] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,



$10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, and  $10^{-15}$  M.

### *Gene Therapy*

[0298] In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[0299] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[0300] For general reviews of the methods of gene therapy, see Goldspiel et al., *Clinical Pharmacy* 12:488-505 (1993); Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, *TIBTECH* 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); and Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990).

[0301] In a preferred embodiment, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, *Proc. Natl.*

Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

[0302] Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids *in vitro*, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or ex vivo gene therapy.

[0303] In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

[0304] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., *Meth. Enzymol.* 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Kiem et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

[0305] Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143- 155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

[0306] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Patent No. 5,436,146).

[0307] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

[0308] In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, *Meth. Enzymol.* 217:599-618 (1993); Cohen et al., *Meth. Enzymol.* 217:618-644 (1993); Cline, *Pharmac. Ther.* 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

[0309] The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

[0310] Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to, epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

- [0311] In a preferred embodiment, the cell used for gene therapy is autologous to the patient.
- [0312] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered *in vivo* for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained *in vitro* can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).
- [0313] In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by the presence or absence of an appropriate inducer of transcription.

*Demonstration of Therapeutic or Prophylactic Activity*

- [0314] The compounds or pharmaceutical compositions of the invention are preferably tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, *in vitro* assays which can be used to determine whether administration of a specific compound is indicated, include *in vitro* cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

*Therapeutic/Prophylactic Administration and Composition*

[0315] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred embodiment, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

[0316] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

[0317] Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0318] In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local

infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[0319] In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

[0320] In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., *Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); see also Levy et al., *Science* 228:190 (1985); During et al., *Ann. Neurol.* 25:351 (1989); Howard et al., *J.Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984)).

[0321] Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

[0322] In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use

of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0323] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide



the form for proper administration to the patient. The formulation should suit the mode of administration.

[0324] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0325] The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0326] The amount of the compound of the invention, which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0327] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a

patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

[0328] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

#### *Diagnosis and Imaging*

[0329] Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

[0330] The invention provides a diagnostic assay for diagnosing a musculoskeletal system disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a

particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0331] Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0332] One facet of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. A preferred embodiment of the invention is the detection and diagnosis of a disease or disorder of the musculoskeletal system associated with aberrant expression of a musculoskeletal system antigen in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide

of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[0333] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of <sup>99m</sup>Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0334] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0335] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disorder, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[0336] Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0337] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al.,

U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

### *Kits*

[0338] The present invention provides kits that can be used in the above methods.

In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody, which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

[0339] In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum-containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope, which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine, which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

[0340] In a more specific embodiment, the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

[0341] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum-containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[0342] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

[0343] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

[0344] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

### **Uses of the Polynucleotides**

[0345] Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

[0346] The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art. Table 1A, column 8 provides the chromosome location of some of the polynucleotides of the invention.

[0347] Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

[0348] Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends

Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

[0349] Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

[0350] For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

[0351] Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 1A and/or Table 2 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

[0352] The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999), each of which is hereby incorporated by reference in its entirety.

[0353] Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library).) Column 9 of Table 1A provides an OMIM reference identification number of diseases associated with the cytologic band disclosed in column 8 of Table 1A, as determined using techniques described herein and by reference to Table 5. Assuming 1 megabase mapping resolution and one gene per 20



kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

[0354] Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicate that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

[0355] Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker. Diagnostic and prognostic methods, kits and reagents encompassed by the present invention are briefly described below and more thoroughly elsewhere herein (see e.g., the sections labeled "Antibodies", "Diagnostic Assays", and "Methods for Detecting Musculoskeletal System Disease, Including Cancer").

[0356] Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder. Additional non-limiting examples of diagnostic methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., Example 12).

[0357] In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject, as further described herein. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will

specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31'-mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

[0358] Where a diagnosis of a related disorder, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[0359] By "measuring the expression level of polynucleotides of the invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the related disorder or being determined by averaging levels from a population of individuals not having a related disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[0360] By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains polypeptide of the present invention or the corresponding mRNA. As indicated, biological samples include body fluids (such as semen, lymph, vaginal pool, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and tissue sources found to express the polypeptide of the present invention. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0361] The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are attached to a solid support. In one exemplary method, the support may be a “gene chip” or a “biological chip” as described in U.S. Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with polynucleotides of the invention attached may be used to identify polymorphisms between the isolated polynucleotide sequences of the invention, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e., their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, digestive disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. Such a method is described in U.S. Patents 5,858,659 and 5,856,104. The U.S. Patents referenced *supra* are hereby incorporated by reference in their entirety herein.

[0362] The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by Nielsen et al., *Science* 254:1497 (1991); and Egholm et al., *Nature* 365:666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with

PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point ( $T_{sub.m}$ ) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

[0363] The compounds of the present invention have uses, which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[0364] The compounds of the present invention have preferred uses, which include, but are not limited to, detecting cancer of musculoskeletal system tissues in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: osteochondroma, benign chondroma, chondroblastoma, chondromyxoid fibroma, osteoid osteoma, giant cell tumor, multiple myeloma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's tumor, and malignant lymphoma of bone. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[0365] Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Gelman, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in *Neoplastic Diseases of the Blood*, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Gelman et al., *supra*) It is likely that mutated or altered expression of specific genes is involved in the

pathogenesis of some leukemias, among other tissues and cell types. (Gelmann et al., *supra*) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Gelmann et al., *supra*)

[0366] For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not be limited to treatment, prevention, diagnosis and/or prognosis, of proliferative disorders of cells and tissues of hematopoietic origin, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes. In preferred embodiments, the compounds and/or methods of the invention are used to treat, prevent, diagnose, and/or prognose, proliferative disorders of musculoskeletal system cells and tissues.

[0367] In addition to the foregoing, a polynucleotide of the present invention can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself

(antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions. Non-limiting antisense and triple helix methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the section labeled "Antisense and Ribozyme (Antagonists)").

[0368] Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell. Additional non-limiting examples of gene therapy methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the sections labeled "Gene Therapy Methods" and Examples 16, 17 and 18).

[0369] The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

[0370] The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

[0371] Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

[0372] There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers prepared from the sequences of the present invention, specific to tissues, including but not limited to, those sequences referred to in Table 1A. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination. Additional non-limiting examples of such uses are further described herein.

[0373] Because musculoskeletal system antigens are found expressed in musculoskeletal system tissues, the polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed

to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In a specific embodiment, the polynucleotides of the present invention are also useful as hybridization probes for differential identification of musculoskeletal system tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of musculoskeletal system tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, for example, normal musculoskeletal system tissues or diseased musculoskeletal system tissues, and/or those tissues/cells corresponding to the library source relating to a polynucleotide sequence of the invention as disclosed in column 7 of Table 1A, and/or cancerous and/or wounded tissues) or bodily fluids (e.g., semen, lymph, vaginal pool, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

[0374] Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of a disorder.

[0375] In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.



**Uses of the Polypeptides**

[0376] Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

[0377] Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

[0378] Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (see, e.g., Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0379] In addition to assaying levels of polypeptide of the present invention in a biological sample, proteins can also be detected *in vivo* by imaging. Antibody labels or markers for *in vivo* imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

[0380] A musculoskeletal system antigen-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example,  $^{131}\text{I}$ ,  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ , ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ,  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for musculoskeletal system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of  $^{99\text{m}}\text{Tc}$ . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0381] In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0382] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

[0383] In a preferred embodiment, the invention provides a method for the specific destruction of musculoskeletal system cells (e.g., aberrant musculoskeletal system cells, musculoskeletal system neoplasm) by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) in association with toxins or cytotoxic prodrugs. In another preferred embodiment the invention provides a method for the specific destruction of tissues/cells corresponding to the library source relating to a polynucleotide sequence of the invention as disclosed in column 7 of Table 1A by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

[0384] By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,  $^{213}\text{Bi}$ , or other radioisotopes such as, for example,  $^{103}\text{Pd}$ ,  $^{133}\text{Xe}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$ ,  $^{68}\text{Ge}$ ,  $^{57}\text{Co}$ ,  $^{65}\text{Zn}$ ,  $^{85}\text{Sr}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{90}\text{Y}$ ,  $^{153}\text{Sm}$ ,  $^{153}\text{Gd}$ ,  $^{169}\text{Yb}$ ,  $^{51}\text{Cr}$ ,  $^{54}\text{Mn}$ ,  $^{75}\text{Se}$ ,  $^{113}\text{Sn}$ ,  $^{90}\text{Yttrium}$ ,  $^{117}\text{Tin}$ ,  $^{186}\text{Rhenium}$ ,  $^{166}\text{Holmium}$ , and  $^{188}\text{Rhenium}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0385] In a specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope  $^{90}\text{Y}$ . In another specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope  $^{111}\text{In}$ . In a further specific embodiment, the invention provides a method for the

specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope  $^{131}\text{I}$ .

[0386] Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

[0387] Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0388] Moreover, polypeptides of the present invention can be used to treat or prevent diseases or conditions of the musculoskeletal system such as, for example, bone disorders (e.g., osteoporosis, osteomyelitis, Paget's disease, and sciolosis); joint disorders (e.g., osteoarthritis, rheumatoid arthritis, infectious arthritis, systemic lupus erythematosus, gout, and Reiter's syndrome); ligament, tendon, and bursa disorders (e.g., bursitis, tendinitis, and tenosynovitis); muscle disorders (e.g., muscular dystrophy, Pompe's disease, periodic paralysis, polymyalgia rheumatica, polymyositis, and Steinert's disease), neoplasms and/or cancers of musculoskeletal tissues (e.g., osteochondroma, benign chondroma, chondroblastoma, osteoid osteoma, and giant cell tumor), and/or those disorders described under "Musculoskeletal System Disorders". In preferred embodiments, polynucleotides expressed in a particular tissue type (see,

e.g., Table 1A, column 7) are used to diagnose, detect, prevent, treat and/or prognose disorders associated with the tissue type. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

[0389] Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described *supra*, and elsewhere herein). For example, administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

[0390] At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the biological activities described herein.

### **Diagnostic Assays**

[0391] The compounds of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various musculoskeletal system related disorders in mammals, preferably humans. Such disorders include, but are not limited to bone disorders (e.g., osteoporosis, osteomyelitis, Paget's disease, and sciolosis); joint disorders (e.g., osteoarthritis, rheumatoid arthritis, infectious arthritis, systemic lupus erythematosus, gout, and Reiter's syndrome); ligament, tendon, and bursa disorders

(e.g., bursitis, tendinitis, and tenosynovitis); muscle disorders (e.g., muscular dystrophy, Pompe's disease, periodic paralysis, polymyalgia rheumatica, polymyositis, and Steinert's disease), neoplasms and/or cancers of musculoskeletal tissues (e.g., osteochondroma, benign chondroma, chondroblastoma, osteoid osteoma, and giant cell tumor), and/or those disorders described under "Musculoskeletal System Disorders". In preferred embodiments, polynucleotides expressed in a particular tissue type (see, e.g., Table 1A, column 7) are used to diagnose, detect, prevent, treat and/or prognose disorders associated with the tissue type.

[0392] Musculoskeletal system antigens are expressed in the musculoskeletal system, with an increased expression level in musculoskeletal system tissues. For a number of musculoskeletal system-related disorders, substantially altered (increased or decreased) levels of musculoskeletal system antigen gene expression can be detected in musculoskeletal system tissue or other cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" musculoskeletal system antigen gene expression level, that is, the musculoskeletal system antigen expression level in musculoskeletal system tissues or bodily fluids from an individual not having the musculoskeletal system disorder. Thus, the invention provides a diagnostic method useful during diagnosis of a musculoskeletal system disorder, which involves measuring the expression level of the gene encoding the musculoskeletal system associated polypeptide in musculoskeletal system tissue or other cells or body fluid from an individual and comparing the measured gene expression level with a standard musculoskeletal system antigens gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a musculoskeletal system disorder.

[0393] In specific embodiments, the invention provides a diagnostic method useful during diagnosis of a disorder of a normal or diseased tissue/cell source corresponding to column 7 of Table 1A, which involves measuring the expression level of the coding sequence of a polynucleotide sequence associated with this tissue/cell source as disclosed in Table 1A in the tissue/cell source or other cells or body fluid from an individual and comparing the expression level of the coding sequence with a standard expression level of the coding sequence of a polynucleotide sequence, whereby an

increase or decrease in the gene expression level(s) compared to the standard is indicative of a disorder of a normal or diseased tissue/cell source corresponding to column 7 of Table 1A.

[0394] In particular, it is believed that certain tissues in mammals with cancer of cells or tissue of the musculoskeletal system express significantly enhanced or reduced levels of normal or altered musculoskeletal system antigen expression and mRNA encoding the musculoskeletal system associated polypeptide when compared to a corresponding "standard" level. Further, it is believed that enhanced or depressed levels of the musculoskeletal system associated polypeptide can be detected in certain body fluids (e.g., sera, plasma, urine, and spinal fluid) or cells or tissue from mammals with such a cancer when compared to sera from mammals of the same species not having the cancer.

[0395] For example, as disclosed herein, musculoskeletal system associated polypeptides of the invention are expressed in musculoskeletal system tissues. Accordingly, polynucleotides of the invention (e.g., polynucleotide sequences complementary to all or a portion of a musculoskeletal system antigen mRNA nucleotide sequence of SEQ ID NO:X, nucleotide sequence encoding SEQ ID NO:Y, nucleotide sequence encoding a polypeptide encoded by SEQ ID NO:X and/or a nucleotide sequence delineated by columns 8 and 9 of Table 2) and antibodies (and antibody fragments) directed against the polypeptides of the invention may be used to quantitate or qualitate concentrations of cells of the musculoskeletal system expressing musculoskeletal system antigens, preferably on their cell surfaces. These polynucleotides and antibodies additionally have diagnostic applications in detecting abnormalities in the level of musculoskeletal system antigens gene expression, or abnormalities in the structure and/or temporal, tissue, cellular, or subcellular location of musculoskeletal system antigens. These diagnostic assays may be performed *in vivo* or *in vitro*, such as, for example, on blood samples, biopsy tissue or autopsy tissue. In specific embodiments, polynucleotides and antibodies of the invention are used to quantitate or qualitate tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding musculoskeletal system sequence disclosed in the same row of Table 1A, preferably on their cell surface.

[0396] Thus, the invention provides a diagnostic method useful during diagnosis of a musculoskeletal system disorder, including cancers, which involves measuring the expression level of the gene encoding the musculoskeletal system antigen polypeptide in musculoskeletal system tissue or other cells or body fluid from an individual and comparing the measured gene expression level with a standard musculoskeletal system antigen gene expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a musculoskeletal system disorder. In specific embodiments, polynucleotides and antibodies of the invention are used to quantitate or qualitate tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding musculoskeletal system sequence disclosed in the same row of Table 1A, preferably on their cell surface.

[0397] Where a diagnosis of a disorder in the musculoskeletal system, including diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed musculoskeletal system antigen gene expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[0398] By "assaying the expression level of the gene encoding the musculoskeletal system associated polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the musculoskeletal system antigen polypeptide or the level of the mRNA encoding the musculoskeletal system antigen polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the musculoskeletal system associated polypeptide level or mRNA level in a second biological sample). Preferably, the musculoskeletal system antigen polypeptide expression level or mRNA level in the first biological sample is measured or estimated and compared to a standard musculoskeletal system antigen polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having a disorder of the musculoskeletal system. As will be appreciated in the art, once a standard musculoskeletal system antigen polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.



[0399] By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source containing musculoskeletal system antigen polypeptides (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid) which contain cells expressing musculoskeletal system antigen polypeptides, musculoskeletal system tissue, and other tissue sources found to express the full length or fragments thereof of a musculoskeletal system antigen. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0400] Total cellular RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, *Anal. Biochem.* 162:156-159 (1987). Levels of mRNA encoding the musculoskeletal system antigen polypeptides are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

[0401] The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of musculoskeletal system antigen polypeptides, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of musculoskeletal system antigens compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide, such as a musculoskeletal system antigen polypeptide of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying musculoskeletal system antigen polypeptide levels in a biological sample can occur using any art-known method.

[0402] Assaying musculoskeletal system antigen polypeptide levels in a biological sample can occur using antibody-based techniques. For example, musculoskeletal system antigen polypeptide expression in tissues can be studied with classical

immunohistological methods (Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting musculoskeletal system antigen polypeptide gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99\text{m}}\text{Tc}$ ), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0403] The tissue or cell type to be analyzed will generally include those, which are known, or suspected, to express the musculoskeletal system antigen gene (such as, for example, cells of the musculoskeletal system or cancer of musculoskeletal system tissues). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the musculoskeletal system antigen gene.

[0404] For example, antibodies, or fragments of antibodies, such as those described herein, may be used to quantitatively or qualitatively detect the presence of musculoskeletal system antigen gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0405] In a preferred embodiment, antibodies, or fragments of antibodies directed to any one or all of the predicted epitope domains of the musculoskeletal system antigen polypeptides (Shown in Table 1A, column 6) may be used to quantitatively or qualitatively detect the presence of musculoskeletal system antigen gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled

antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0406] In an additional preferred embodiment, antibodies, or fragments of antibodies directed to a conformational epitope of a musculoskeletal system antigen may be used to quantitatively or qualitatively detect the presence of musculoskeletal system antigen gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0407] The antibodies (or fragments thereof), and/or musculoskeletal system antigen polypeptides of the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of musculoskeletal system antigen gene products or conserved variants or peptide fragments thereof. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or musculoskeletal system antigen polypeptide of the present invention. The antibody (or fragment thereof) or musculoskeletal system antigen polypeptide is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the musculoskeletal system antigen gene product, or conserved variants or peptide fragments, or musculoskeletal system antigen polypeptide binding, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

[0408] Immunoassays and non-immunoassays for musculoskeletal system antigen gene products or conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of binding musculoskeletal system antigen gene products or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

[0409] The biological sample may be brought in contact with and immobilized

onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled anti-musculoskeletal system antigen antibody or detectable musculoskeletal system antigen polypeptide. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or polypeptide. Optionally the antibody is subsequently labeled. The amount of bound label on solid support may then be detected by conventional means.

[0410] By "solid phase support or carrier" is intended any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

[0411] The binding activity of a given lot of anti-musculoskeletal system antigen antibody or musculoskeletal system antigen polypeptide may be determined according to well-known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

[0412] In addition to assaying musculoskeletal system antigen polypeptide levels or polynucleotide levels in a biological sample obtained from an individual, musculoskeletal system antigen polypeptide or polynucleotide can also be detected *in vivo* by imaging. For example, in one embodiment of the invention, musculoskeletal system antigen polypeptide and/or anti-musculoskeletal system antigen antibodies are used to image musculoskeletal system diseased cells, such as neoplasms. In another

embodiment, musculoskeletal system antigen polynucleotides of the invention (e.g., polynucleotides complementary to all or a portion of musculoskeletal system antigen mRNA) and/or anti-musculoskeletal system antigen antibodies (e.g., antibodies directed to any one or a combination of the epitopes of musculoskeletal system antigens, antibodies directed to a conformational epitope of musculoskeletal system antigens, antibodies directed to the full length polypeptide expressed on the cell surface of a mammalian cell) are used to image diseased or neoplastic cells of the musculoskeletal system.

[0413] Antibody labels or markers for *in vivo* imaging of musculoskeletal system antigen polypeptides include those detectable by X-radiography, NMR, MRI, CAT-scans or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. Where *in vivo* imaging is used to detect enhanced levels of musculoskeletal system antigen polypeptides for diagnosis in humans, it may be preferable to use human antibodies or "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using techniques described herein or otherwise known in the art. For example methods for producing chimeric antibodies are known in the art. See, for review, Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., *Nature* 312:643 (1984); Neuberger et al., *Nature* 314:268 (1985).

[0414] Additionally, any musculoskeletal system antigen polypeptides whose presence can be detected, can be administered. For example, musculoskeletal system antigen polypeptides labeled with a radio-opaque or other appropriate compound can be administered and visualized *in vivo*, as discussed, above for labeled antibodies. Further such musculoskeletal system antigen polypeptides can be utilized for *in vitro* diagnostic procedures.

[0415] A musculoskeletal system antigen polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging

moiety, such as a radioisotope (for example,  $^{131}\text{I}$ ,  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ ), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a musculoskeletal system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of  $^{99\text{m}}\text{Tc}$ . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain musculoskeletal system antigen protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0416] With respect to antibodies, one of the ways in which the anti-musculoskeletal system antigen antibody can be detectably labeled is by linking the same to an enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., *J. Clin. Pathol.* 31:507-520 (1978); Butler, J.E., *Meth. Enzymol.* 73:482-523 (1981); Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL.; Ishikawa, E. et al., (eds.), 1981, Enzyme Immunoassay, Kigaku Shoin, Tokyo). The enzyme, which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods, which employ a chromogenic substrate for the enzyme. Detection may also be accomplished

by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

[0417] Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect musculoskeletal system antigens through the use of a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

[0418] It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescamine.

[0419] The antibody can also be detectably labeled using fluorescence emitting metals such as  $^{152}\text{Eu}$ , or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentaacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

[0420] The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

[0421] Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

**Methods for Detecting Musculoskeletal System Disease, Including Cancer**

[0422] In general, a musculoskeletal system disease or cancer may be detected in a patient based on the presence of one or more musculoskeletal system antigen proteins of the invention and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine, and/or tumor biopsies) obtained from the patient. In other words, such proteins and/or polynucleotides may be used as markers to indicate the presence or absence of a musculoskeletal system disease or disorder, including cancer. Cancers that may be diagnosed, and/or prognosed using the compositions of the invention include but are not limited to, cancer of musculoskeletal system tissues. In addition, such proteins and/or polynucleotides may be useful for the detection of other diseases and cancers, including cancers of tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding musculoskeletal system sequence disclosed in the same row of Table 1A. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding musculoskeletal system antigen polypeptides, which is also indicative of the presence or absence of a musculoskeletal system disease or disorder, including cancer. In general, musculoskeletal system antigen polypeptides should be present at a level that is at least three fold higher in diseased tissue than in normal tissue.

[0423] There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *supra*. In general, the presence or absence of a musculoskeletal system disease in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

[0424] In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the musculoskeletal system antigen polypeptide of the invention from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection



reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include musculoskeletal system antigen polypeptides and portions thereof, or antibodies, to which the binding agent binds, as described above.

[0425] The solid support may be any material known to those of skill in the art to which musculoskeletal system antigen polypeptides of the invention may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for the suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 ug, and preferably about 100 ng to about 1 ug, is sufficient to immobilize an adequate amount of binding agent.

[0426] Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with

both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

### **Gene Therapy Methods**

[0427] Also encompassed by the present invention are gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of a musculoskeletal system antigen of the present invention. This method requires a polynucleotide, which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

[0428] Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldegrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells, which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

[0429] As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[0430] In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

[0431] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

[0432] Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

[0433] Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[0434] The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[0435] For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

[0436] The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or

bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[0437] The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

[0438] The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

[0439] In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

[0440] Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy]propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y., (see, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

[0441] Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of

DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

[0442] Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphosphatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[0443] For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

[0444] The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a

homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include  $\text{Ca}^{2+}$ -EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta (1975) 394:483; Wilson et al., Cell 17:77 (1979); ether injection (Deamer, D. and Bangham, A., Biochim. Biophys. Acta 443:629 (1976); Ostro et al., Biochem. Biophys. Res. Commun. 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA 76:3348 (1979)); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem. 255:10431 (1980); Szoka et al., Proc. Natl. Acad. Sci. USA 75:145 (1978); Schaefer-Ridder et al., Science 215:166 (1982)), which are herein incorporated by reference.

[0445] Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

[0446] U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and International Publication No. WO 94/9469 provide methods for delivering DNA-cationic lipid complexes to mammals.

[0447] In certain embodiments, cells are engineered, *ex vivo* or *in vivo*, using a retroviral particle containing RNA, which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia

Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

[0448] The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and CaPO<sub>4</sub> precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

[0449] The producer cell line generates infectious retroviral vector particles, which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express a polypeptide of the present invention.

[0450] In certain other embodiments, cells are engineered, *ex vivo* or *in vivo*, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz, et al., Am. Rev. Respir. Dis.109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143-155 (1991)). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green et al., Proc. Natl. Acad. Sci. USA 76:6606 (1979)).



[0451] Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, *Curr. Opin. Genet. Devel.* 3:499-503 (1993); Rosenfeld et al., *Cell* 68:143-155 (1992); Engelhardt et al., *Human Genet. Ther.* 4:759-769 (1993); Yang et al., *Nature Genet.* 7:362-369 (1994); Wilson et al., *Nature* 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express E1a and E1b, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

[0452] Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest, which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

[0453] In certain other embodiments, the cells are engineered, *ex vivo* or *in vivo*, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., *Curr. Topics in Microbiol. Immunol.* 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

[0454] For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus,

using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles, which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either *ex vivo* or *in vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

[0455] Another method of gene therapy involves operably associating heterologous control regions and endogenous musculoskeletal system antigen polynucleotide sequences (e.g., encoding a musculoskeletal system antigen polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), which are herein incorporated by reference. This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

[0456] Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

[0457] The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the

amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

[0458] The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

[0459] The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

[0460] The polynucleotide encoding a polypeptide of the present invention may contain a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the musculoskeletal system antigen polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

[0461] Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppository solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

[0462] A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

[0463] Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

[0464] Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site. In specific embodiments, suitable delivery vehicles for use with systemic administration comprise liposomes comprising polypeptides of the invention for targeting the vehicle to a particular site.

[0465] Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

[0466] Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of

treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

[0467] Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

### **Biological Activities**

[0468] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat, prevent diagnose and/or prognose the associated disease.

[0469] The musculoskeletal system antigen polynucleotides and polypeptides of the invention are predicted to have predominant expression in musculoskeletal system tissues.

[0470] Thus, the musculoskeletal system antigens of the invention may be useful as therapeutic molecules. Each would be useful for diagnosis, detection, treatment and/or prevention of diseases or disorders of the musculoskeletal system, including but not limited to bone disorders (e.g., osteoporosis, osteomyelitis, Paget's disease, and sciolosis); joint disorders (e.g., osteoarthritis, rheumatoid arthritis, infectious arthritis, systemic lupus erythematosus, gout, and Reiter's syndrome); ligament, tendon, and bursa disorders (e.g., bursitis, tendinitis, and tenosynovitis); muscle disorders (e.g., muscular dystrophy, Pompe's disease, periodic paralysis, polymyalgia rheumatica, polymyositis, and Steinert's disease), neoplasms and/or cancers of musculoskeletal tissues (e.g., osteochondroma, benign chondroma, chondroblastoma, osteoid osteoma, and giant cell tumor), and/or those disorders described under "Musculoskeletal System Disorders".

[0471] In a preferred embodiment, polynucleotides of the invention (e.g., a nucleic acid sequence of SEQ ID NO:X or the complement thereof; or the cDNA sequence contained in Clone ID NO:Z, or fragments or variants thereof) and/or polypeptides of the invention (e.g., an amino acid sequence contained in SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, or the complement thereof, an amino acid sequence encoded by the cDNA sequence contained in Clone ID NO:Z and fragments or variants thereof as described herein) are useful for the diagnosis, detection, treatment, and/or prevention of diseases or disorders of the tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding musculoskeletal system sequence disclosed in the same row of Table 1A.

[0472] Particularly, the musculoskeletal system antigens may be a useful therapeutic for cancer of musculoskeletal system tissues. Treatment, diagnosis, detection, and/or prevention of musculoskeletal system disorders could be carried out using a musculoskeletal system antigen or soluble form of a musculoskeletal system antigen, a musculoskeletal system antigen ligand, gene therapy, or ex vivo applications. Moreover, inhibitors of a musculoskeletal system antigen, either blocking antibodies or mutant forms, could modulate the expression of the musculoskeletal system antigen. These inhibitors may be useful to treat, diagnose, detect, and/or prevent diseases associated with the misregulation of a musculoskeletal system antigen.

[0473] In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells (e.g., normal or diseased musculoskeletal system cells) by administering polypeptides of the invention (e.g., musculoskeletal system antigen polypeptides or anti-musculoskeletal system antigen antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell (e.g., an aberrant musculoskeletal system cell or musculoskeletal system cancer cell). In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0474] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of aberrant musculoskeletal system cells, including, but not limited to, musculoskeletal system tumor cells) by administering polypeptides of the invention (e.g., musculoskeletal system antigen polypeptides or fragments thereof, or anti-musculoskeletal system antigen antibodies) in association with toxins or cytotoxic prodrugs.

[0475] By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, cytotoxins (cytotoxic agents), or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, <sup>213</sup>Bi, or other radioisotopes such as, for example, <sup>103</sup>Pd, <sup>133</sup>Xe, <sup>131</sup>I, <sup>68</sup>Ge, <sup>57</sup>Co, <sup>65</sup>Zn, <sup>85</sup>Sr, <sup>32</sup>P, <sup>35</sup>S, <sup>90</sup>Y, <sup>153</sup>Sm, <sup>153</sup>Gd, <sup>169</sup>Yb, <sup>51</sup>Cr, <sup>54</sup>Mn, <sup>75</sup>Se, <sup>113</sup>Sn, <sup>90</sup>Yttrium, <sup>117</sup>Tin, <sup>186</sup>Rhenium, <sup>166</sup>Holmium, and <sup>188</sup>Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0476] Techniques known in the art may be applied to label antibodies of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety). A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine,

tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0477] By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

[0478] It will be appreciated that conditions caused by a decrease in the standard or normal level of a musculoskeletal system antigen activity in an individual, particularly disorders of the musculoskeletal system, can be treated by administration of a musculoskeletal system antigen polypeptide (e.g., such as, for example, the complete musculoskeletal system antigen polypeptide, the soluble form of the extracellular domain of a musculoskeletal system antigen polypeptide, or cells expressing the complete protein) or agonist. Thus, the invention also provides a method of treatment of an individual in need of an increased level of musculoskeletal system antigen activity comprising administering to such an individual a pharmaceutical composition comprising an amount of an isolated musculoskeletal system antigen polypeptide of the invention, or agonist thereof (e.g., an agonistic anti-musculoskeletal system antigen antibody), effective to increase the musculoskeletal system antigen activity level in such an individual.

[0479] It will also be appreciated that conditions caused by a increase in the standard or normal level of musculoskeletal system antigen activity in an individual, particularly disorders of the musculoskeletal system, can be treated by administration of musculoskeletal system antigen polypeptides (e.g., such as, for example, the



complete musculoskeletal system antigen polypeptide, the soluble form of the extracellular domain of a musculoskeletal system antigen polypeptide, or cells expressing the complete protein) or antagonist (e.g., an antagonistic musculoskeletal system antigen antibody). Thus, the invention also provides a method of treatment of an individual in need of an decreased level of musculoskeletal system antigen activity comprising administering to such an individual a pharmaceutical composition comprising an amount of an isolated musculoskeletal system antigen polypeptide of the invention, or antagonist thereof (e.g., an antagonistic anti-musculoskeletal system antigen antibody), effective to decrease the musculoskeletal system antigen activity level in such an individual.

[0480] In certain embodiments, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 7 (Tissue Distribution Library Code).

[0481] More generally, polynucleotides, translation products and antibodies corresponding to this gene may be useful for the diagnosis, prognosis, prevention, and/or treatment of diseases and/or disorders associated with the following systems.

#### **Musculoskeletal System Disorders**

[0482] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the musculoskeletal system, including but not limited to, disorders of the bone, joints, ligaments, tendons, bursa, muscle, and/or neoplasms and cancers associated with musculoskeletal tissue.

[0483] Diseases or disorders of the bone include, but are not limited to, Albers-Schönberg disease, bowlegs, heel spurs, Köhler's bone disease, knock-knees, Legg-Calvé-Perthes disease, Marfan's syndrome, mucopolysaccharidoses, Osgood-Schlatter disease, osteochondroses, osteochondrodysplasia, osteomyelitis, osteopetroses,

osteoporosis (postmenopausal, senile, and juvenile), Paget's disease, Scheuermann's disease, scoliosis, Sever's disease, and patellofemoral stress syndrome.

[0484] Joint diseases or disorders include, but are not limited to, ankylosing spondylitis, Behçet's syndrome, CREST syndrome, Ehlers-Danlos syndrome, infectious arthritis, discoid lupus erythematosus, systemic lupus erythematosus, Lyme disease, osteoarthritis, psoriatic arthritis, relapsing polychondritis, Reiter's syndrome, rheumatoid arthritis (adult and juvenile), scleroderma, and Still's disease.

[0485] Diseases or disorders affecting ligaments, tendons, or bursa include, but are not limited to, ankle sprain, bursitis, posterior Achilles tendon bursitis (Haglund's deformity), anterior Achilles tendon bursitis (Albert's disease), tendinitis, tenosynovitis, popliteus tendinitis, Achilles tendinitis, medial or lateral epicondylitis, rotator cuff tendinitis, spasmodic torticollis, and fibromyalgia syndrome.

[0486] Muscle diseases or disorders include, but are not limited to, Becker's muscular dystrophy, Duchenne's muscular dystrophy, Landouzy-Dejerine muscular dystrophy, Leyden-Möbius muscular dystrophy, Erb's muscular dystrophy, Charcot's joints, dermatomyositis, gout, pseudogout, glycogen storage diseases, Pompe's disease, mitochondrial myopathy, periodic paralysis, polymyalgia rheumatica, polymyositis, Steinert's disease, Thomsen's disease, anterolateral and posteromedial shin splints, posterior femoral muscle strain, and fibromyositis.

[0487] Musculoskeletal tissue may also develop cancers and/or neoplasms that include, but are not limited to, osteochondroma, benign chondroma, chondroblastoma, chondromyxoid fibroma, osteoid osteoma, giant cell tumor, multiple myeloma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's tumor, and malignant lymphoma of bone.

### **Immune Activity**

[0488] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and

macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

[0489] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to treat diseases and disorders of the immune system and/or to inhibit or enhance an immune response generated by cells associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 7 (Tissue Distribution Library Code).

[0490] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing, and/or prognosing immunodeficiencies, including both congenital and acquired immunodeficiencies. Examples of B cell immunodeficiencies in which immunoglobulin levels B cell function and/or B cell numbers are decreased include: X-linked agammaglobulinemia (Bruton's disease), X-linked infantile agammaglobulinemia, X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, X-linked lymphoproliferative syndrome (XLP), agammaglobulinemia including congenital and acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, unspecified hypogammaglobulinemia, recessive agammaglobulinemia (Swiss type), Selective IgM deficiency, selective IgA deficiency, selective IgG subclass deficiencies, IgG subclass deficiency (with or without IgA deficiency), Ig deficiency with increased IgM, IgG and IgA deficiency with increased IgM, antibody deficiency with normal or elevated Igs, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), common variable immunodeficiency (CVID), common variable immunodeficiency (CVI) (acquired), and transient hypogammaglobulinemia of infancy.

[0491] In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are treated, prevented, diagnosed, and/or prognosing using

the polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof.

[0492] Examples of congenital immunodeficiencies in which T cell and/or B cell function and/or number is decreased include, but are not limited to: DiGeorge anomaly, severe combined immunodeficiencies (SCID) (including, but not limited to, X-linked SCID, autosomal recessive SCID, adenosine deaminase deficiency, purine nucleoside phosphorylase (PNP) deficiency, Class II MHC deficiency (Bare lymphocyte syndrome), Wiskott-Aldrich syndrome, and ataxia telangiectasia), thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity.

[0493] In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, or antagonists or agonists thereof.

[0494] Other immunodeficiencies that may be treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, include, but are not limited to, chronic granulomatous disease, Chédiak-Higashi syndrome, myeloperoxidase deficiency, leukocyte glucose-6-phosphate dehydrogenase deficiency, X-linked lymphoproliferative syndrome (XLP), leukocyte adhesion deficiency, complement component deficiencies (including C1, C2, C3, C4, C5, C6, C7, C8 and/or C9 deficiencies), reticular dysgenesis, thymic aplasia, immunodeficiency with thymoma, severe congenital leukopenia, dysplasia with immunodeficiency, neonatal neutropenia, short limbed dwarfism, and Nezelof syndrome-combined immunodeficiency with Igs.

[0495] In a preferred embodiment, the immunodeficiencies and/or conditions associated with the immunodeficiencies recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0496] In a preferred embodiment polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among immunodeficient individuals. In specific

embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

[0497] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides and polypeptides of the invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

[0498] Autoimmune diseases or disorders that may be treated, prevented, diagnosed and/or prognosed by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, one or more of the following: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, hemolytic anemia, thrombocytopenia, autoimmune thrombocytopenia purpura, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, purpura (e.g., Henloch-Scoenlein purpura), autoimmunocytopenia, Goodpasture's syndrome, Pemphigus vulgaris, myasthenia gravis, Grave's disease (hyperthyroidism), and insulin-resistant diabetes mellitus.

[0499] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome, autoimmune pulmonary inflammation, autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

[0500] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the

invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

[0501] Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiomyopathy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

[0502] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention. In a specific

preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0503] In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0504] In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0505] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0506] In preferred embodiments, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a immunosuppressive agent(s).

[0507] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia. Alternatively, Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or

conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

[0508] Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, diagnosed and/or prognosed using polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

[0509] Additionally, polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, may be used to treat, prevent, diagnose and/or prognose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

[0510] Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1.), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass



complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

[0511] Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, polynucleotides, polypeptides, and antibodies of the invention, as well as agonists or antagonists thereof, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adenitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chorditis, cochitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myositis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

[0512] In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or

chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

[0513] In other embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

[0514] Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

[0515] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance tumor-specific immune responses.

[0516] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from

the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

[0517] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

[0518] In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Meissneria meningitidis*, *Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi*.

[0519] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria) or Leishmania.

[0520] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

- [0521] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.
- [0522] In one embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.
- [0523] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell responsiveness to pathogens.
- [0524] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an activator of T cells.
- [0525] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.
- [0526] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to induce higher affinity antibodies.
- [0527] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to increase serum immunoglobulin concentrations.
- [0528] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to accelerate recovery of immunocompromised individuals.

[0529] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

[0530] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

[0531] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

[0532] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

[0533] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one

embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonism of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

[0534] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

[0535] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

[0536] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodeficiency.

[0537] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in the pretreatment of bone marrow samples prior to transplant.

[0538] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence/immunodeficiency such as observed among SCID patients.

[0539] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of

activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

[0540] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

[0541] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in one or more of the applications described herein, as they may apply to veterinary medicine.

[0542] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

[0543] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

[0544] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

[0545] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

[0546] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed for instance

to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.

[0547] The polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.

[0548] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit complement mediated cell lysis.

[0549] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.

[0550] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

[0551] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed to treat adult respiratory distress syndrome (ARDS).

[0552] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.

[0553] In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or



prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with polynucleotides or polypeptides, and/or agonists of the present invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

[0554] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

[0555] In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic leukemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

[0556] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

[0557] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

[0558] In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

[0559] Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see, e.g., Example 9). Agonists of the invention include, for example, binding or stimulatory antibodies, and soluble forms of the polypeptides (e.g., Fc fusion proteins; see, e.g., Example 9). polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

[0560] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741). Administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention to such animals is useful for the generation of monoclonal antibodies against the polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention.

### **Blood-Related Disorders**

[0561] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hemostatic (the stopping

of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists or antagonists of the present invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

[0562] In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, diagnose, prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used for the prevention of occlusion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

[0563] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 7 (Tissue Distribution Library Code).

[0564] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets.. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for example eosinophilia.

[0565] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, treat, or diagnose blood dyscrasia.

[0566] Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary siderob;astic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune helolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The polynucleotides,

polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyl dopa, dapsone, and/or sulfadiazine. Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

[0567] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to major and minor forms of alpha-thalassemia and beta-thalassemia.

[0568] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak syndromes, thromboxane A<sub>2</sub> dysfunction, thromboasthenia, and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophelias such as hemophilia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary Hemorrhagic Telangiectasia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

[0569] The effect of the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention on the clotting time of blood may be monitored using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or the Lee-White Clotting time.

[0570] Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in a specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

[0571] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders characterized by or associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body generates increased numbers of white blood cells during infection. Thus, leukocytosis may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer. Leukocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis

[0572] Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia. Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency), neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment, anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

[0573] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies, and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndrome, severe combined immunodeficiency, ataxia telangiectasia).

[0574] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

[0575] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

[0576] In yet another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphoblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukemia), chronic myelocytic (myeloid, myelogenous, or granulocytic) leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

[0577] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

[0578] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myeloid metaplasia, thrombocythemia, (including both primary and secondary thrombocythemia) and chronic myelocytic leukemia.

[0579] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as a treatment prior to surgery, to increase blood cell production.



[0580] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosinophils and macrophages.

[0581] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

[0582] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase cytokine production.

[0583] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

#### **Hyperproliferative Disorders**

[0584] Musculoskeletal system associated polynucleotides or polypeptides, or agonists or antagonists thereof, can be used to treat, prevent, diagnose and/or prognose hyperproliferative diseases, disorders, and/or conditions, including neoplasms.

[0585] In a specific embodiment, musculoskeletal system associated polynucleotides or polypeptides, or agonists or antagonists thereof, can be used to treat, prevent, and/or diagnose hyperproliferative diseases, disorders, and/or conditions of the musculoskeletal system.

[0586] In a preferred embodiment, musculoskeletal system associated polynucleotides or polypeptides, or agonists or antagonists thereof, can be used to treat, prevent, and/or diagnose neoplasms of musculoskeletal system tissues.

[0587] Musculoskeletal system associated polynucleotides or polypeptides, or agonists or antagonists of the invention, may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, musculoskeletal system

associated polynucleotides or polypeptides, or agonists or antagonists thereof, may proliferate other cells, which can inhibit the hyperproliferative disorder.

[0588] For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative diseases, disorders, and/or conditions can be treated, prevented, and/or diagnosed. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating, preventing, and/or diagnosing hyperproliferative diseases, disorders, and/or conditions, such as a chemotherapeutic agent.

[0589] Examples of hyperproliferative diseases, disorders, and/or conditions that can be treated, prevented, and/or diagnosed by musculoskeletal system associated polynucleotides or polypeptides, or agonists or antagonists thereof, include, but are not limited to neoplasms located in the: prostate, colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

[0590] Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia,

Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias,

Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0591] In another preferred embodiment, polynucleotides or polypeptides, or agonists or antagonists of the present invention are used to diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

[0592] Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal

epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous hyperplasia, and verrucous hyperplasia.

[0593] Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

[0594] Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, anhidrotic ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atrioidigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, facioidigitogenital dysplasia, familial fibrous dysplasia of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid

osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, oculovertbral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

[0595] Additional pre-neoplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

[0596] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, 7 (Tissue Distribution Library Code).

[0597] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including, but not limited to those described herein. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat acute myelogenous leukemia.

[0598] Additionally, polynucleotides, polypeptides, and/or agonists or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated

by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[0599] In preferred embodiments, polynucleotides, polypeptides, and/or agonists or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

[0600] Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous

gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[0601] Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

[0602] Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

[0603] Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders,



paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0604] One preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

[0605] Thus, the present invention provides a method for treating cell proliferative diseases, disorders, and/or conditions by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said cell proliferation, disease, disorder, and/or condition.

[0606] In a preferred embodiment, the present invention provides a method for treating cell proliferative diseases, disorders and/or conditions of the musculoskeletal system by inserting into a cell, a polynucleotide of the present invention, wherein said polynucleotide represses said cell proliferation, disease and/or disorder.

[0607] Another embodiment of the present invention provides a method of treating cell-proliferative diseases, disorders, and/or conditions in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (see, e.g., G J. Nabel, et. al., PNAS 96: 324-326 (1999), which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e., magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e., to